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TREATMENT OF EXPERIMENTAL RENAL HYPERTENSION WITH PARTIALLY PURIFIED RENIN

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IN 1941, two of us[1] reported that daily intramuscular injections of partially purified hog renin for four months produced striking reductions in the blood pressures of dogs with experimental renal (Goldblatt) hypertension, whereas heat-inactivated hog renin and active dog renin were without antipressor effect. Moreover, daily intramuscular injections of hog renin solution into two dogs for three months before and three months after constriction of the renal arteries prevented the development of hypertension. The serums of the dogs treated with hog renin, but not the serums of the dogs that received injections of inactivated hog renin or dog renin, neutralized the acute pressor effect of renin (antirenin). In this report, we emphasized the fact that additional experiments were necessary in order to establish definitely the prophylactic and therapeutic value of renin solutions in experimental renal hypertension in the dog, as well as to clarify the mechanisms involved.

Experiments have now been completed in which the prophylactic effects of hog renin, inactivated hog renin, dog renin, rabbit renin, inactive human renin, and an extract of liver have been studied. Moreover, we have investigated the therapeutic effects of a second course of hog renin on hypertensive dogs that had previously been successfully treated with hog renin, and also the therapeutic effects of hog renin on hypertensive dogs which did not show an antipressor response to a previous course of inactivated hog renin or active dog renin, respectively.[1] These prophylactic and therapeutic experiments constitute the basis for the present report.

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METHODS

The methods used were, in general, similar to those previously employed.[1] Mean blood pressure readings were obtained by puncture of a femoral artery (method of Dameshek and Loman[2]) two or three times a week. Studies on the blood urea nitrogen, urinalyses, and determinations of the body weight were made at monthly or bimonthly intervals, and more frequently when indicated. With the exception of one experiment with highly purified hog renin, the method used for the preparation of the renin solutions was essentially that described by Grossman,[3] except that acetone was employed as a dehydrating agent, and much of the associated protein was removed by isoelectric precipitation. These renin solutions were therefore *only partially purified, and obviously contained substances other than renin.* The highly purified renin was prepared from the partially purified renin by the method of one of us,[4] using a series of precipitations which removed 84 per cent of the nonrenin substances without appreciably affecting the amount of pressor activity. With two exceptions, the renin solutions were equivalent to 1 Gm. of fresh kidney cortex per c.c. of solution. In the case of highly purified hog renin, however, the solution was equivalent to 5 Gm. of fresh kidney cortex per c.c. of solution, and when the dosage of partially purified hog renin was doubled in certain therapeutic experiments, the solution was equivalent to 2 Gm. of fresh kidney cortex per c.c. of solution. All of the renin solutions contained 0.5 per cent phenol.

Treatment consisted of daily intramuscular injections of the renin solutions. Unless otherwise stated, the dosage was 1 Gm. of fresh kidney cortex equivalent per kg. of body weight. In the prophylactic experiments, the dogs were treated with renin solutions for a period of approximately six months. In the middle of this period the right and left renal arteries were constricted, three weeks apart, by the Goldblatt technique.[5] Four dogs were treated with hog renin, four with hog renin inactivated by heating at 70° C. for one-half hour, four with dog renin, two with rabbit renin, two with inactive human renin (renal extract prepared like renin, but pressor inactive), and three with liver extract prepared after the manner of renin. In the therapeutic experiments, unless otherwise stated, a course of renin therapy occupied a period of four months. All of the seven hypertensive dogs in this group had previously been subjected to one course of renin injections, and the results reported.[1] For four of the dogs this first course consisted of hog renin; for two, inactivated hog renin; and for one, dog renin. In the experiments reported here, all of these dogs were given hog renin injections.

Blood serums were examined for antirenin before treatment, and subsequently during treatment, at semimonthly intervals, and, after treatment, at monthly and bimonthly intervals. The technique, previously described,[6] consisted essentially in mixing two volumes of serum with one volume of renin solution, allowing the mixture to stand at least overnight at 4° C., and assaying the acute pressor effect produced by giving the mixture intravenously to the etherized, nephrectomized dog. The dose of renin solution was 0.25 Gm. of kidney cortex equivalent per kg. of assay animal. In all instances the serum tested for antirenin was suitably controlled with serum from untreated, normal dogs, and frequently with serum from untreated hypertensive dogs. Antirenin titers were regularly ascertained for dog renin, less frequently for hog renin, and exceptionally (two dogs receiving rabbit renin) for rabbit renin.

RESULTS

I. Prophylactic Experiments.—

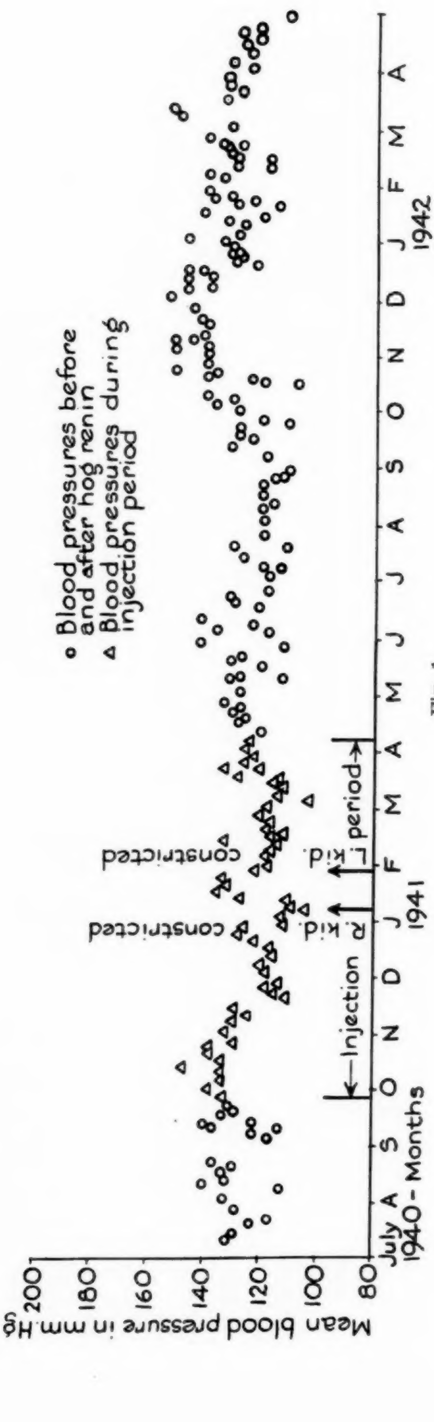
Hog Renin.—During three months of hog renin injections prior to constriction of the renal arteries, the blood pressures of the four dogs in this group showed no significant change from the normal levels observed during a preceding control period of two to three months. Sub-

sequent to constriction of the renal arteries, two of the dogs showed no important change in blood pressure during the remaining three months of treatment with hog renin or during observation periods of eleven and thirteen months, respectively, after renin therapy. The results with one of these two dogs are shown in Fig. 1. The third dog showed a very moderate, but significant, rise in blood pressure after constriction of the renal arteries, with a gradual increase in the hypertension during the seven months of observation subsequent to treatment. After constriction of the renal arteries, the fourth dog developed pronounced hypertension which persisted without essential alteration during the seven months of observation subsequent to the injections of hog renin (Fig. 2).

Inactivated Hog Renin.—During the three months of inactivated hog renin injections prior to constriction of the renal arteries, the blood pressures of the four dogs remained at the normal levels that obtained during the initial control period of two and one-half months. One dog continued to have a normal blood pressure despite the renal artery constrictions. Normal pressure persisted in this animal during three months of continued inactivated hog renin injections and seven months of subsequent observation. After constriction of the renal arteries, hypertension developed in the three remaining dogs. No significant changes occurred in the hypertension of these three dogs during the ensuing three months of continued inactivated hog renin injections or during the seven months of observation after the completion of the injections.

Dog Renin.—There were no significant deviations from the initial control levels in the blood pressures of this group of four dogs during the three months of injections of dog renin prior to bilateral renal artery constriction. Two of the dogs continued to have a normal blood pressure after renal artery constriction. The blood pressure of one of these continued to be normal during the three months of continued dog renin treatment and during the seven months of observation subsequent to dog renin injections. The other animal's pressure remained within normal limits during the period of dog renin injections after the arterial constrictions, but showed a gradual, though significant, rise in blood pressure during the seven months succeeding dog renin injections. The two remaining dogs developed hypertension after the arterial constrictions. The hypertension of these two animals continued essentially unchanged during three months of continued dog renin injections and seven months of observation subsequent to the termination of the injections.

Rabbit Renin.—The normal pressure of the two dogs in this group was not altered during the first three months of rabbit renin injections. After constriction of the renal arteries the pressures continued to be normal. Shortly after constriction of the second renal artery, one of the two dogs died of pneumonia. The other animal retained a persistently normal pressure, not only during the three additional months of rabbit



Mean blood pressure in mm. Hg
200
180
160
140
120
100
80
July 1940 - Months
A S O N D J F M A M J J A S O N D J F M A
1941
1942
R. kid. constricted
L. kid. constricted
←Injection period→
○ Blood pressures before and after hog renin
△ Blood pressures during injection period

Fig. 1.

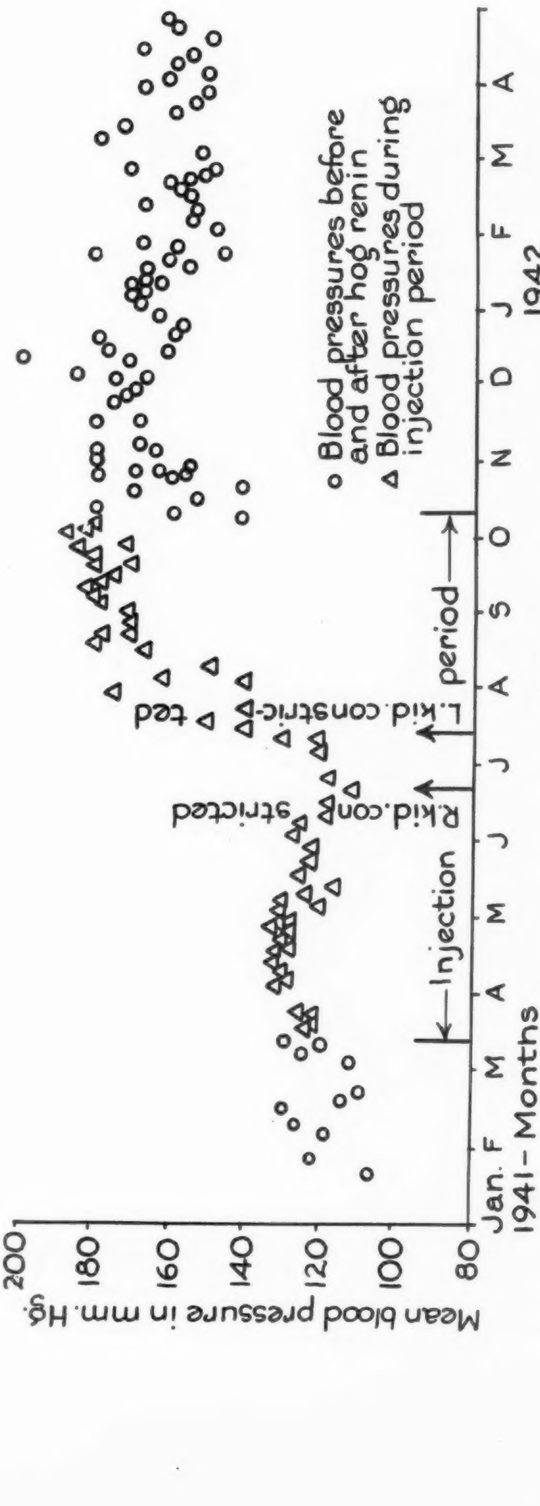

Mean blood pressure in mm. Hg.
200
180
160
140
120
100
80
Jan. F M A M J J A S O N D J F M A
1941-Months
1942
Injection period
R.kid.constricted
L.kid.constricted
Blood pressures before and after hog renin
Blood pressures during injection period

Fig. 2.

renin injections, but also during the seven months subsequent to rabbit renin treatment.

Inactive Human Renin.—The normal pressure of two dogs during the initial control period was unchanged by three months of inactive human renin injections prior to constriction of the renal arteries. Renal artery constriction produced hypertension in both animals, and one of the dogs died of malignant hypertension two weeks subsequent to the arterial constriction. The hypertension of the other animal persisted during the remaining three months of inactive human renin injections and during the three months which have elapsed since treatment was stopped.

Liver Extract.—The normal pressure of the three dogs in this group did not show any significant changes during the preconstriction injection period. After constriction of the renal arteries, all three of the dogs developed hypertension. Two weeks subsequent to the second operation, one of the dogs died of malignant hypertension. The other two dogs have shown no significant change in their hypertension during the postconstriction injection period.

Untreated Controls.—After two to four months of control blood pressure readings, sixteen dogs were subjected to bilateral renal artery constriction. After the constrictions, all of the dogs developed hypertension. These control dogs showed persistent hypertension during the five to seven months of observation subsequent to constriction.

Antirenin became demonstrable in the serums of the four dogs that received hog renin and the two dogs which were given rabbit renin during the second month of treatment, and disappeared during the second month, after treatment was discontinued. Antirenin assays were repeatedly negative in the dogs which received inactivated hog renin, dog renin, inactive human renin, and liver extract, as well as in the untreated controls.

No toxic effects from the injections were detected in any of the animals. Their appetites remained excellent, their weights constant, and their blood urea nitrogen and urine normal, throughout.

II. THERAPEUTIC EXPERIMENTS.—

Hog Renin (Preceded by Hog Renin).—The first hypertensive dog showed a decrease in blood pressure to normal or even subnormal levels during the first course of hog renin treatment. After the completion of therapy there was a slow return over a period of seven months to the pretreatment hypertensive range, where the pressure remained for the next five months that concluded the period of observation reported in our previous communication.[1] During the succeeding five months, however, the blood pressure of this animal fluctuated from normal to definitely hypertensive levels. Then the second course of hog renin injections was begun. These fluctuations in blood pressure have continued without noteworthy change during the six months of treatment, despite doubling of the hog renin dosage during the last three months (Fig. 3).

The second dog showed a decrease in blood pressure to the normal level during the first course of hog renin therapy, with a gradual increase during the four months after treatment to a hypertensive level approximately 20 mm. Hg below the pretreatment hypertensive range. During the succeeding four months the dog's pressure continued unchanged; this concluded the period of observation reported in our previous communication.[1] Four months subsequently, with the hypertensive level unaltered, the dog was subjected to a second course of hog renin. Again a prompt decrease in blood pressure to low normal levels occurred. Three months after the completion of the second course the pressure was still normal, although it then began to rise (Fig. 4).

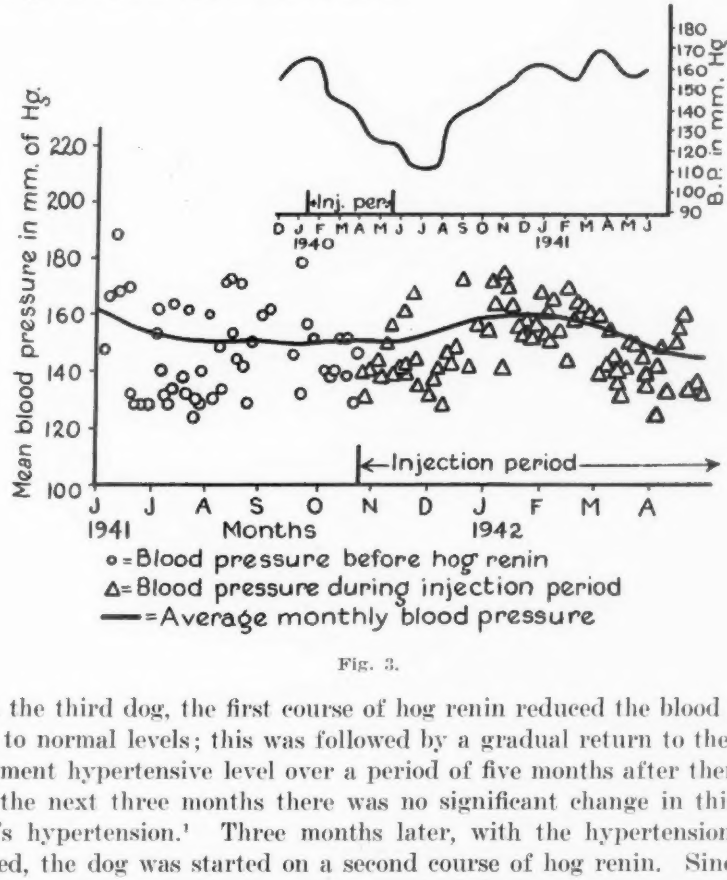
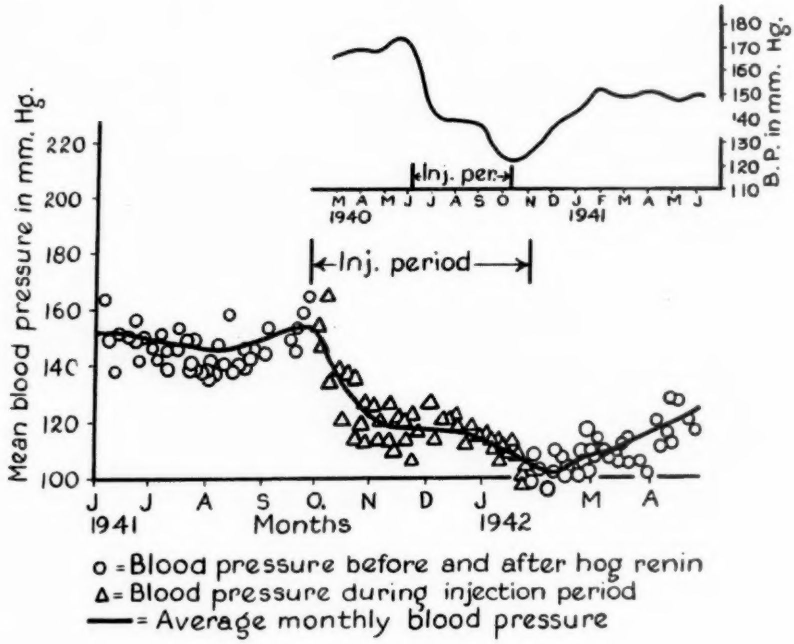


Fig. 3.

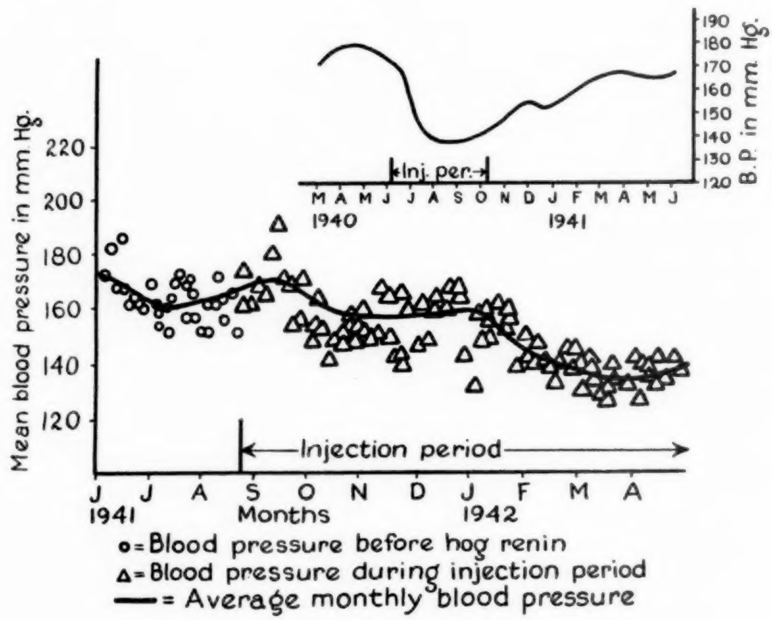
In the third dog, the first course of hog renin reduced the blood pressure to normal levels; this was followed by a gradual return to the pretreatment hypertensive level over a period of five months after therapy. For the next three months there was no significant change in this animal's hypertension.[1] Three months later, with the hypertension unaltered, the dog was started on a second course of hog renin. Since no significant change in blood pressure resulted during the four months of treatment, the hog renin dosage was doubled. Four additional months of therapy at this dosage have resulted in a decrease in blood pressure to normal levels (Fig. 5).

The fourth dog showed a significant reduction in blood pressure, although not to normal levels, as a result of the first course of hog renin. Subsequent to treatment the blood pressure returned to its pretreatment



Mean blood pressure in mm. Hg.
220
200
180
160
140
120
100
Inj. period
J J A S O N D J M A
1941 Months 1942
Inj. per.
M A M J J A S O N D J F M A M J
1940 1941
180
170
160
150
140
130
120
110
B.P. in mm. Hg.
o = Blood pressure before and after hog renin
Δ = Blood pressure during injection period
— = Average monthly blood pressure

Fig. 4.



Mean blood pressure in mm. Hg.
220
200
180
160
140
120
Injection period
J J A S O N D J F M A
1941 Months 1942
Inj. per.
M A M J J A S O N D J F M A M J
1940 1941
190
180
170
160
150
140
130
120
B.P. in mm. Hg.
o = Blood pressure before hog renin
Δ = Blood pressure during injection period
— = Average monthly blood pressure

Fig. 5.

hypertensive level over a period of four months, where it remained during the next four months.[1] Two months later, the dog was given a second course of hog renin. This produced a reduction in blood pressure strikingly similar to that which resulted from the first course. Subsequent to therapy, the pressure gradually increased to the pretreatment hypertensive level over a period of five months (Fig. 6).

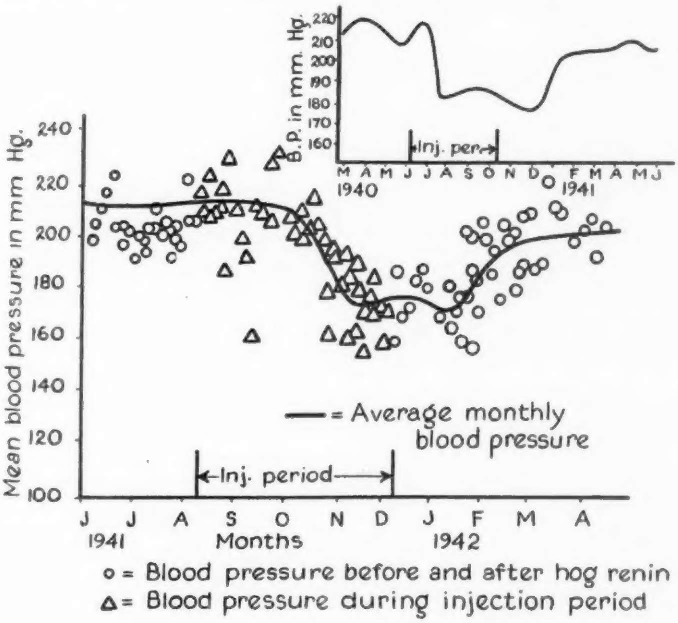


Fig. 6.

Antirenin became demonstrable in the serums of these four dogs during the second month of the first course of hog renin therapy. Antirenin disappeared from the first dog during the seventeenth month after treatment, whereas the renin neutralizing body was no longer demonstrable in the other three dogs by the seventh, fifth, and sixth months, respectively, after treatment.[1] After instituting the second course of hog renin, antirenin reappeared in the serums of the four dogs during the second week of therapy. The first and third dogs are still under treatment, and, obviously, antirenin continues to be present. Antirenin has persisted to date in the second and fourth dogs, three and five months, respectively, after the completion of treatment.

Hog Renin (Preceded by Inactivated Hog Renin).—The first hypertensive dog of this group showed no significant change in blood pressure as a consequence of a course of inactivated hog renin injections.[1] Two weeks later, an eight months' course of highly purified hog renin was instituted. Since this produced no significant effect, it was followed by a course of partially purified hog renin, which produced a slight, but probably significant, decrease in blood pressure during the fourth

month. However, when the dosage of partially purified hog renin was then doubled, a gradual reduction in blood pressure to the normal level for the animal occurred during the ensuing three months of treatment with the larger dose (Fig. 7).

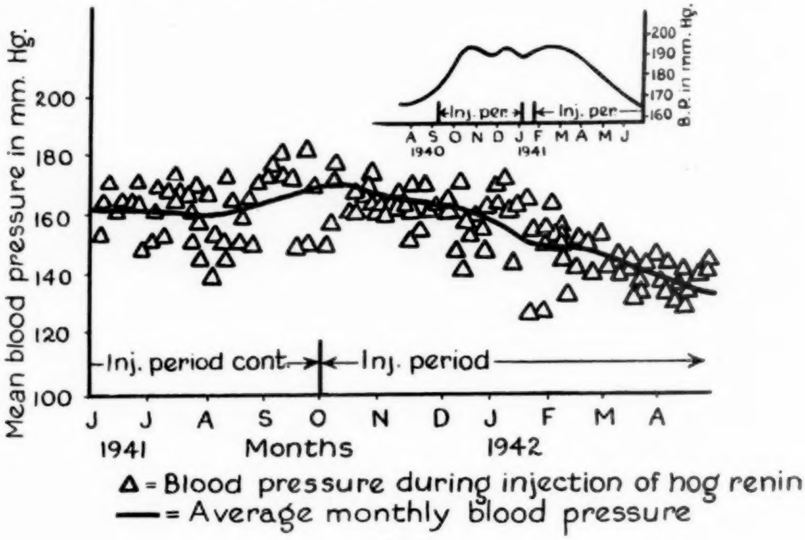


Fig. 7.

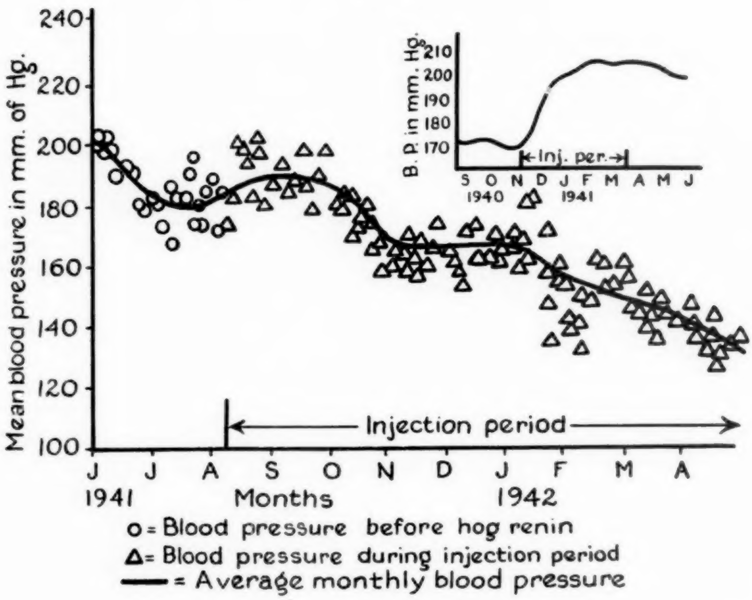


Fig. 8.

The second dog likewise showed no significant change in blood pressure during or following a course of inactivated hog renin.[1] Two weeks after the inactivated hog renin, the dog was given an eight months'

course of hog renin in one-quarter the usual dosage, without any effect on the animal's hypertension. Subsequent to this, and, for the past seven months, the dog has been used for the assay (with negative results) of the antipressor action of a different type of kidney extract, not germane to the present discussion.

No antirenin developed in the serums of these two dogs as a result of the inactivated hog renin injections.[1] During the second month of (active) hog renin, however, antirenin became demonstrable in both dogs. The renin neutralizing body has persisted to date in the first dog, which is still under therapy, but disappeared from the serum of the second animal during the third month after treatment with hog renin was discontinued.

Hog Renin (Preceded by Dog Renin).—One dog showed a significant increase of approximately 30 mm. Hg in its hypertension during an initial course of dog renin.[1] The blood pressure gradually decreased to the pretreatment hypertensive range over a period of five months after dog renin. The dog was then given a five months' course of hog renin without any significant effect on the hypertension. When the dosage of hog renin was doubled, the blood pressure of the animal gradually decreased to normal levels during four months of additional therapy with the larger dose (Fig. 8).

The course of dog renin did not result in the appearance of antirenin in the serum of this dog.[1] During the second month of hog renin injections, however, antirenin became demonstrable, and persisted during nine months of hog renin treatment.

As previously reported for the first courses of injections which these seven hypertensive dogs received,[1] the later courses of treatment with the hog renins reported in this communication were without any detectable local or general toxic effects.

COMMENT

The prophylactic experiments constitute the first successful prevention of experimental renal hypertension in the dog; a number of unsuccessful attempts have previously been reported. Thus, renal artery denervation,[7-9] splanchnicotomy,[10] anterior root section,[11] buffer nerve section,[12] complete sympathectomy,[13-15] and destruction of the spinal cord below the fifth cervical segment[16] did not prevent the development of experimental renal hypertension after constriction of the renal arteries in dogs. Page and Sweet[17] found that previous hypophysectomy in dogs decreased the hypertension resulting from renal artery constriction, but did not prevent it. Thyroidectomy[18] and gonadectomy[19] did not interfere with the production of experimental renal hypertension. Collins and Wood[20] reported that adrenalectomy diminished, but did not prevent, the hypertension consequent upon renal artery constriction in dogs. Page, Patton, and Ogden[21] found that pregnancy frequently delayed the onset of experimental renal hypertension in rats.

Our results show that, of a total of fifteen dogs treated with renal extracts, six (40 per cent) were protected against hypertension and nine were not. This is in striking contrast to the control group of sixteen untreated dogs, all of which became hypertensive. In a larger series of 75 untreated dogs which were operated upon by essentially the same technique during the past three years, we have failed to obtain some degree of hypertension in only one animal. Others[22] have reported failure to obtain hypertension after constriction of the renal arteries by a somewhat different technique in 10 per cent of their dogs.

The long periods of normal pressure in five of the protected dogs after the discontinuance of treatment are striking. We intend to observe these animals for a minimum of eighteen months subsequent to treatment. If these five dogs do not become hypertensive during this observation period, we shall further constrict the renal arteries until hypertension, malignant hypertension, or fatal uremia without hypertension results. The fact that only one per cent of our untreated dogs failed to develop at least some degree of hypertension after constriction of the renal arteries renders most unlikely the possibility that the persistence of normal pressure was unrelated to the renal extracts injected. That they constitute true instances of successful prophylaxis is also attested by the fact that one dog which received dog renin was protected only during the period of treatment, and that one dog that was partially protected by hog renin showed a further increase in blood pressure after treatment.

The mechanism of these prophylactic effects is not apparent at present. Obviously, the small number of animals in each prophylactic group and the lack of consistent results within each group make a final interpretation impossible. Whether the prophylactic effects are due to *renin or to some other substance or substances in the partially purified solutions* is likewise not ascertainable at present. The evidence that the prophylactic effects are not brought about by antirenin appears conclusive. Thus, two dogs which received dog renin and one that was given inactivated hog renin were protected against experimental renal hypertension, although these animals never at any time showed antirenin in their serums. Furthermore, the two dogs treated with hog renin and the one treated with rabbit renin, which were protected against hypertension, continued to have a normal pressure for months after the disappearance of antirenin from their serums. Nevertheless, some other type of antihormone or immune response is not completely ruled out.

The results of the therapeutic experiments amply confirm the previously reported effectiveness of hog renin solution in experimental renal hypertension in the dog. Thus, the second and fourth dogs, which received two courses of hog renin, again showed a decrease in blood pressure to normal levels as a consequence of the second course of hog renin. The third dog responded to the second course of hog renin after the dosage was doubled. The first dog has thus far not responded even to

an increased hog renin dosage, although this animal obtained an excellent therapeutic result from the first course of hog renin. Of the two dogs which had previously received a course of inactivated hog renin without showing any antipressor effect, one did not respond to highly purified hog renin or to partially purified hog renin, but did respond with a decrease in blood pressure to normal when the partially purified hog renin dosage was doubled. The other dog did not respond to hog renin in reduced dosage. The dog which had previously received a course of dog renin without antipressor effect regained normal blood pressure under a course of hog renin, although only after the dosage was doubled.

The mechanism of these reductions in blood pressure which are produced in experimental renal hypertension by hog renin is not yet clear. Whether the therapeutic effects of hog renin are due to *renin or to some other principle or principles in the partially purified solution* cannot be stated at present. The recent statement by Friedman, et al.,[23] that highly purified hog renin is without antipressor effect in renal hypertensive dogs is wholly inconclusive in this connection, for the dose which they employed was only one-twentieth of our minimum in terms of renin, although the same in terms of fresh kidney cortex equivalent. Almost certainly, our therapeutic effects were not due to antirenin. Thus, in the first hypertensive dog, which received two courses of hog renin, the blood pressure returned to the pretreatment hypertensive level after the first course, in spite of the persistence of antirenin in the serum. Moreover, despite the prompt reappearance of antirenin during the second course, there has thus far been no significant reduction of this animal's blood pressure. The third dog, which received two courses of hog renin, showed no therapeutic effects from the second course of hog renin, despite the prompt reappearance of antirenin, until the dosage of hog renin was doubled. Likewise, the two dogs that were first treated with inactivated hog renin did not show therapeutic effects after eight months of highly purified hog renin or eight months of partially purified hog renin (in reduced dosage), respectively, although antirenin became demonstrable in their serums during the second month of treatment with the hog renins. Similarly, the hypertensive dog which first received a course of dog renin showed no therapeutic response from the course of hog renin until the dosage was doubled, although antirenin was produced by the initial hog renin dosage.

As stated above, we observed a notable lack of toxic effects from the injections of these kidney extracts into both normal and hypertensive dogs, although the most sensitive tests for renal, hepatic, and other functions were not employed. The toxic effects of partially purified renin solutions noted by Winternitz, et al.,[24] and Leiter and Eichelberger[25] are probably related chiefly to their employment of the intravenous route. All of our injections were given intramuscularly. Moreover, the toxic substances demonstrated by Winternitz and Leiter in their partially purified kidney extracts are not necessarily related in any way to the

prophylactically and therapeutically potent principle or principles in the renal extracts which we have employed.

In order to ascertain the active principle or principles in these renal extracts, we must conduct studies on larger groups of dogs, treated prophylactically and therapeutically with partially purified renin solutions and with highly purified renins. The effect of dosage, which has been briefly investigated in some of the therapeutic experiments reported above, as well as the effect of route of administration, must also be studied further. These investigations are in process.

If future results substantiate the continued promise of our observations to date, we shall study the effect of this type of treatment in essential hypertension in man.

CONCLUSIONS

1. For the first time, experimental renal hypertension was prevented in six of fifteen dogs by the daily intramuscular injection of certain partially purified renin solutions for three months before, and three months after, constriction of the renal arteries. Two of four dogs were protected by hog renin, one of four by heat-inactivated hog renin, two of four by dog renin, one out of one by rabbit renin, and none of two by inactive human renin.

2. Liver extract, prepared like partially purified renin, offered no protection to three dogs; all of sixteen untreated control animals developed experimental renal hypertension after constriction of the renal arteries.

3. Daily intramuscular injections of partially purified hog renin solution for four months or more produced striking reductions in the blood pressure of renal hypertensive dogs. Three of four animals showed therapeutic responses to a second course of hog renin equal to the excelcellent effects which resulted from a course of hog renin administered one year before. One dog which had previously received a course of inactivated hog renin, and one that had previously been given dog renin, without antipressor effect in both cases, showed reductions in blood pressure to normal levels during a subsequent course of hog renin.

4. The mechanism of these prophylactic and therapeutic effects is not now apparent. They may be due to renin or to some other substance or substances in the partially purified renal extracts. Antirenin is almost certainly not involved.

5. Attempts to identify the active principle or principles in the renin solutions and to clarify the mechanisms involved are being made.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

I. Factors Which Affect Its Direction and Its Relation to the Mean QRS Axis

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With an Appendix on Notation by R. H. Bayley, M.D.†

In 1934, Wilson, Barker, Macleod, and Johnston[1] published an important paper dealing with the areas of the ventricular deflections of the human electrocardiogram. It was shown that the net area of the QRS-T, above or below the isoelectric line, in any two limb leads, could be used to calculate the direction and magnitude of the manifest area of QRS-T. Since it possesses both direction and magnitude, this quantity is a vector and was called the ventricular gradient by Wilson, Macleod, and Barker.[2] The papers cited give a fairly detailed explanation of the QRS-T vector, and to them the reader is referred. It will, therefore, be sufficient here to give a briefer explanation.

1. The Nature of the Ventricular Gradient

Fig. 1 shows a sphere of cardiac muscle, lying in a saline solution at the center of an Einthoven triangle. The points in the solution, labeled RA, LA, and LL, are at the corners of the triangle and are equidistant from the muscle. Each pair of points is connected to a galvanometer, in the same fashion as the limb leads are connected to the extremities in human electrocardiography. The three leads will be called Leads I, II, and III. While recording the three leads simultaneously, a stimulus is applied to the surface of the sphere at S. The wave of excitation, thus initiated, progresses through the muscle from the reader's left to the right. During the time of its passage, point RA is negative, point LA is positive, and point LL is, on the average, at zero or earth potential. (Papers which give the experimental evidence for this and other statements in this section are quoted in a textbook.[3]) Consequently, an upward deflection, R, is seen in Lead I, an upward deflection, R, of half the height, in Lead II, and a downward deflection, of the same amplitude as R_2, in Lead III. These waves, like the QRS complex of the human electrocardiogram, are a result of the passage of the wave of depolarization through the muscle. When recorded on the film it is possible to ascertain the area of each wave in microvolt-seconds (m.v.s). With the usual standardization, and time lines 0.04 seconds apart, a potential of 0.1 millivolt, acting upon the galvanometer for 0.04 second, gives a

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small, rectangular deflection of just the size of one of the small time-potential rectangles recorded on the film. This rectangle has a value of 4 m.v.s. Because it is convenient, and obviates one source of error, we have not converted our measurements of area to m.v.s., but refer to each rectangle as a unit of area. We will suppose, for purposes of discussion, that the R wave in Lead I, as recorded from the sphere of muscle, has an area of 10 units. Since the R is upright, we may call it positive, and its area is +10 units. In Lead III, the area of the deflection is –5 units, just half the area of R_1 and opposite in sign. These two quantities, +10 and –5, may now be used to ascertain the direction of the mean axis of this initial deflection. In this example, the direction is 0°, that is, from left to right and parallel to the line of Lead I.

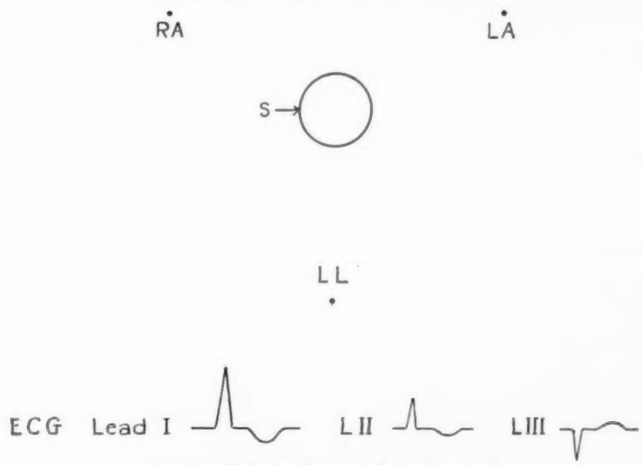

Fig. 1.—This is discussed in the text.

After depolarization of the muscle, repolarization begins. In a physiologically uniform muscle, the area, although not the shape, of the T is the same as the area of the initial deflection, R, but its direction is opposite. In Lead I, the area of the T is –10 units, and, in Lead III, +5 units. The direction of the vector representing T is just opposite to the direction of the R, namely, ±180°. If we add algebraically the areas of the initial and the final deflection in each lead, we will have the net area of the whole diphasic curve, or, in man, the net area of the QRS-T complex. In our experiment, in each lead the algebraic sums are zero. The gradient of the muscle is zero in magnitude and, consequently, has no direction.

Everyone knows that in the normal human ventricular electrocardiogram the net areas of the QRS complex and the T wave in any lead are neither characteristically equal, nor are they opposite in direction. This means, most probably, that the sequences of depolarization and repolarization in man's ventricles are not the same but, usually, about opposite. The result is that the average mean electrical axis of the

QRS complex in man is nearly +60°, and, of the T wave, only about 10° or 12° to the left of this.

Returning to the muscle sphere, it is experimentally an easy matter to reverse the direction of the T wave. All we need to do is to cool the left half of the sphere sufficiently, while keeping the right half uncooled. A stimulus is now applied to the muscle, as before. We will assume, contrary to fact, that the cooling does not change the velocity of the wave of excitation. The initial deflections are then precisely like those derived from the uncooled muscle. In this case, however, the cooled half becomes repolarized much more slowly than the uncooled half of the muscle. Consequently, the right half, which is last to be activated, is now first to recover. The electrical effects of repolarization are reversed, and the T waves are in the same directions as the initial deflections in all leads. If the cooling was just sufficient to produce a T wave of the same area as the R, the net area of R-T, namely QRS-T, in Lead I is now +10 +10, or +20 units, and, in Lead III, −5 and −5, or −10 units. The gradient has a magnitude of 20 units, and a direction of 0°, in this case.

If the upper half of the muscle were cooled instead of the half surrounding the point of stimulation, and cooled to the same temperature as before, the resulting gradient would still possess a magnitude of 20 units, but it would point straight downward, i.e., its direction would be +90°, and at right angles to the direction of the initial deflection.

As we have pointed out, if the sequence of repolarization is the same as that of depolarization, there is no gradient. It is evident, therefore, that the gradient is an expression of those electrical forces which appear when the sequence of repolarization differs from the sequence of depolarization. It may be noted in passing, and this is an important point, that diminution in T-wave amplitude, and even reversals in the T-wave direction and in the electrical axis of the T wave, can result from a mere diminution in the magnitude of the gradient, and may occur under a variety of purely physiologic, as well as pathologic, conditions.

It is possible to record directly the areas from which the gradient is derived. For example, the stimulus may be applied at the geometrical center of the sphere of muscle. The wave of excitation spreads outward in all directions, but the galvanometers record nothing because each electrical force is balanced by an opposing one. No initial deflections appear. But, on repolarization, the uncooled half of the muscle, i.e., that on the left in the figure, becomes repolarized more rapidly than the cooled half, and a large T wave is inscribed in each lead. In Lead I, the area of the T wave is +20 units, and, in Lead III, −10 units, that is, the areas previously derived by adding the areas of the initial and final deflections. The gradient, thus derived, again has a magnitude of +20, and its direction is 0°. It makes no difference where we stimulate the sphere, on the inside or on the outside; the gradient remains unaffected, as the experimental results of Wilson,

Barker, Macleod, and Johnston[1] demonstrated. Furthermore, the time required for passage of the impulse through the muscle will not affect the gradient. Let us suppose that we can cause exactly a 50 per cent increase in the time required by the impulse to invade the muscle in the example of the partly cooled muscle, and again stimulate at S. The R wave in Lead I, since it is twice as wide as before, now has an area of +20, and the net area of the T wave is zero. In Lead III, the area of the initial wave is −10, and the T wave has an area of zero. Similarly, in the human heart, in the two cases of partial bundle branch block in which we have made measurements, the change in intraventricular conduction time from no block to block caused no change in the size or direction of the gradient beyond the limits of error in measurement. There is little change in the gradient in ventricular premature beats, and the change is probably a consequence of the prematurity and the resulting alteration in physiologic state when the early beat occurs.

The ventricular gradient is the fundamental quantity in electrocardiography. A change in the gradient reveals a change in the state of the muscle, as Wilson has emphasized. All T-wave changes which are unassociated with QRS complex changes are caused by changes in the state of the muscle, as in our first example of the cooled muscle. Other T-wave changes are like those in some cases of bundle branch block, and are related to QRS change and not to muscle change. In other cases, both factors operate. It is important to make the distinction; this Wilson has also stated.

2. MEASUREMENT OF THE VENTRICULAR GRADIENT

One thing which has inhibited study of the gradient is the opinion that, unless special methods are employed, its cursory measurement is too inaccurate to be valuable. It is to be noted in this connection that slightly inaccurate quantitative estimations may be vastly preferable to no measurements at all, just as the palpatory method of estimating blood pressure was better than none. There are two things that we wish to know about the gradient, namely, its magnitude and its direction. We find that in most cases the former can be estimated with an error of less than ±10 or ±15 per cent, and the latter with an error of not over ±4 or ±5 degrees. With enough practice, two observers can agree within those limits in the majority of cases. Certain types of records cannot be measured with this degree of accuracy. If the net area of the QRS vector is less than about 4 units, the error in estimating the direction increases, and the error is, in general, inversely proportional to the size of the vector. In this case, even though the percentage error in estimating vector size is large, this is unimportant, for the practically important question is to know whether the vector is small or not. In estimating the size and direction of the gradient, the chief error comes from inaccuracy in placing the base line of the T wave, and particu-

larly in making proper allowance for the magnitude of a normal deviation of the S-T segment, which has been taken as a part of the net T area.

We examine the electrocardiogram with a good reading glass. Following a schema used by Dr. R. H. Bayley, we often estimate the area of an R wave by multiplying its height by half its base, but extreme care must be taken in estimating the width of the base and in allowing for curvature of the ascending or descending limbs. One must also guard against an optical illusion. When an R wave is split by a time line, its ascending and descending limbs appear to be concave; when the R lies between two time lines, its limbs tend to appear convex. The eye also tends to make the base of an R wave which lies between two time lines exactly equal to the time between the lines, although the actual width of the R may be slightly greater or less. These remarks also apply to other waves of good amplitude. The area of R is the area contained within its boundary lines and above the level of the P-R segment at the lower edge of the string shadow. The area of Q is analogously derived, with reference to the upper edge of the P-R segment. The area of S is the inside area below the upper edge of the S-T junction, or, if that junction is deviated, below the level of the base line between T and P, or U and P, if a U is present. The Q and S areas, as negative quantities, are subtracted from the area of R, as a positive quantity, to give the net area of the QRS. The area of T is the net area of any S-T segment shift which may be present and of the T wave proper, so-called. Considerable errors may occur in measuring the T, unless the U-P segments of the cycle before and after the T rest precisely on a horizontal line. Since this condition is not usual, we often measure the apparent areas of two T waves, the base of one which is slightly above, and the base of the other, slightly below, a horizontal millimeter line. The estimate for the one T may, for example, be 5.3 units; for the other, 7.2 units. If the base of one T is apparently just as much below the base line as the other is above, we will be close enough if we call the area 6.2 units. Differences of 0.4 or 0.5 unit in areas of this magnitude have a surprisingly small effect upon vector direction and an unimportant effect on vector size. In those cases in which the net area of QRS in Lead I or in Lead III (which are the leads we use) is nearly zero, and the areas in the other lead are relatively, although not necessarily absolutely, large, the error in estimating the direction of the QRS axis should not be over 1°. One should, of course, make sure that standardization is correct, and, if not, make the proper corrections. In recording the measurements, it is convenient to set down, for each of the two leads chosen, the net QRS area, the T area, and the algebraic sum of these two for the net QRS-T area on one horizontal line. The measurements from the other lead are placed on the line below.

Once the net areas are estimated, they are used to ascertain the directions of the vectors. For this purpose the chart devised by

Dieuaide was used. For estimation of the manifest areas or magnitudes of the vectors, a simple schema is given in Table I. It applies only to vectors derived from Leads I and III.

The directions of the vectors are first ascertained. The following axes are then taken as *bases,* from one of which the axis in question will deviate by 30° or less: 0°, +60°, +120°, ±180°, −120°, −60°.

(a) When the net areas in Lead I and III are both positive or both negative, they are added, and the sum is increased by the following percentages, depending upon the number of degrees of deviation of the axis as ascertained from the nearest *base,* as described in the previous paragraph.

TABLE I

NUMBER OF DEGREES BETWEEN BASIC AXIS AND OBSERVED AXIS	PERCENTAGE INCREASE IN PROJECTED VECTOR LENGTH, TO GIVE THE MANIFEST VALUE
30	15.4
29	14.3
28	13.3
27	12.3
26	11.3
25	10.4
23	8.6
20	6.3
17.5	4.8
15	3.6
10	1.5
5	0.4
0	0

For example, if the net QRS areas are of the same sign in both Leads I and III, they are added. Let us suppose their sum is +7.6 units. We will further suppose that the electrical axis of the QRS is +75°. Now 75° deviates by 15° from the nearest one of the basic axes given above. Hence we add (Table I) 3.6 per cent of 7.6 units to obtain the manifest value of the mean QRS vector. This value is, therefore, 7.8836 units, or, in round numbers, 7.9 units in magnitude. If desired, the figure 7.8836 can be multiplied by 4, giving 31.6 m.v.s. Since the error in measurement is necessarily rather large, it is quite meaningless to employ more than one figure after the decimal place; and, when multiplied by 4, the nearest m.v.s. in value is usually close enough.

(b) When the net area in one lead (I or III) is positive and in the other lead (III or I) is negative, the two are not added, but the value of the largest net area (neglecting its sign) is increased just as in case (a). Suppose that the net area in Lead I is +10 and that, in Lead III, it is −8. The direction is then −20°. This deviates by 20° from 0°, the nearest of the basic axes, as we have called them. In this case the larger value, 10, is multiplied by 106.3 per cent of itself. The manifest value is, therefore, 10.6 units. If the angle happens not to be one given in the table above, one can easily interpolate.

3. THE NATURE OF THE MATERIAL USED

The electrocardiograms used in this study were from 277 persons. The results, which are shown graphically in Fig. 2, were also supported by less careful measurement of about 200 additional electrocardiograms from patients without heart disease. About 50 of the 277 electrocardiograms were from medical students and other normal subjects. The remainder were from patients who, judging from routine hospital examination, were regarded as having no heart disease. Thus it cannot be asserted that all of the patients, particularly the older ones, were without heart disease. A few of our divergent points in Fig. 2 may have come from patients of doubtful cardiac normality. It will become clear, however, that this possibility can have no influence whatever on the correctness of our conclusions, particularly because some of the most discordant points in the figure were from normal controls. Few records from patients over 45 years of age are included. Most of the records were taken with the subject in the recumbent position, but a small number were seated, and one, discussed later, was standing. Electrocardiograms from patients with fever or thyrotoxicosis were excluded. In addition, but not reported in this paper, measurements of the electrocardiograms of several hundred patients with heart disease were made.

Over 200 electrocardiograms were selected at random. The remaining records were chosen because they showed extreme QRS axis deviations for apparently normal subjects. This explains the relatively large number of QRS axes below +10° and above +90°. The proportion shown in the figure would not hold for a purely random sample.

Different records were recorded by means of any one of four string galvanometers used by Charity Hospital or the medical school. The standardization was usually correct. When it was not, the appropriate correction was made, e.g., if 1 mV gave a deflection of 11 mm., the size of the measured area was reduced by 9 per cent, or one-eleventh.

4. FACTORS INFLUENCING THE DIRECTION OF THE NORMAL VENTRICULAR GRADIENT

(a) *Rotation of the Heart About Its Anteroposterior Axis.*—One of the most important of the factors which determine the direction of the ventricular gradient is the position of the heart in the thorax, with reference to its rotation around its anteroposterior axis. This can best be judged by a comparison of the gradient and the heart as seen in the roentgenogram.[6] For purpose of definition, and because the terms are established in the literature, we shall speak of clockwise rotation about the *anteroposterior* axis as rotation to the *right,* and the reverse direction as rotation to the *left,* even though we recognize that the names are illogical. At this time, we cannot make a detailed statement of the relationship between the gradient and rotation to the right or left, but

we can make a few general statements. The gradient of the vertically placed heart is relatively vertical, i.e., usually between +60° and +80°. It is usually more vertical than is the apparent longitudinal anatomic axis of the ventricles. As we shall see, this lack of close correspondence between the anatomic and electrical axes is attributable to the usual rotation of the vertically placed heart about a longitudinal axis. In contrast, the gradient of the transversely placed heart lies much farther to the left than the gradient of the vertical heart, but, again, the correspondence between apparent anatomic axis and electrical axis is not usually precise, and for the same reason. The gradient of the transverse heart is often more transverse than the anatomic axis. It follows that the range in the direction of the gradient is greater than the range in the direction of the anatomic axis, and this difference in range is even more pronounced in the case of the QRS axis. However, these facts must not be taken to mean that the directions indicated by the mean electrical axes deviate greatly from their true directions as these are projected on the frontal plane.

(b) *Rotation of the Heart About a Longitudinal Axis.*—As long ago as 1925, it was shown by Meek and Wilson[4] that rotation of the heart about its long axis produced a marked effect upon the electrocardiogram of the dog. In general, the effects found by them appear to be similar to the effects of rotation of the human heart. For purposes of definition, rotation of the heart about its long axis in a clockwise direction as the heart is viewed from the apex will be referred to as clockwise rotation; and rotation in the opposite direction will be designated counterclockwise rotation. Human hearts which are placed vertically in the thorax are known from anatomic studies usually to be rotated more or less in a clockwise direction, and the majority of such hearts show an S and no Q wave in Lead I, and a Q wave and a small or no S in Lead III. A QRS complex configuration of such a type, whether observed with a vertical or transverse heart, we shall regard as an example of clockwise rotation. In contrast, many transversely placed hearts, as compared with vertical hearts, are known to present a larger area of left ventricular surface when viewed from the front. The electrocardiogram in such cases typically shows a Q wave and no S wave in Lead I, and an S wave and no Q wave in Lead III. We shall regard such electrocardiograms as evidencing counterclockwise rotation. Other electrocardiograms, not quite typical of either type, do, however, betray, fairly clearly, rotation in one direction or the other. Absence of a typical Q wave is the most frequent feature of this group of records. Still other electrocardiograms can be placed in neither group, or show characteristics of both groups. Most of these can be classified as examples of no rotation about a longitudinal axis. Some records show a Q_1 and an S_1 and an M complex in Lead III. This usually means counterclockwise rotation, although, when the middle

portion of the M is shallow, the rotation may be slight or absent. Certain other records show an S wave in the three leads, but no Q waves; or a Q wave in the three leads and no S waves. How these should be classified will be stated below.

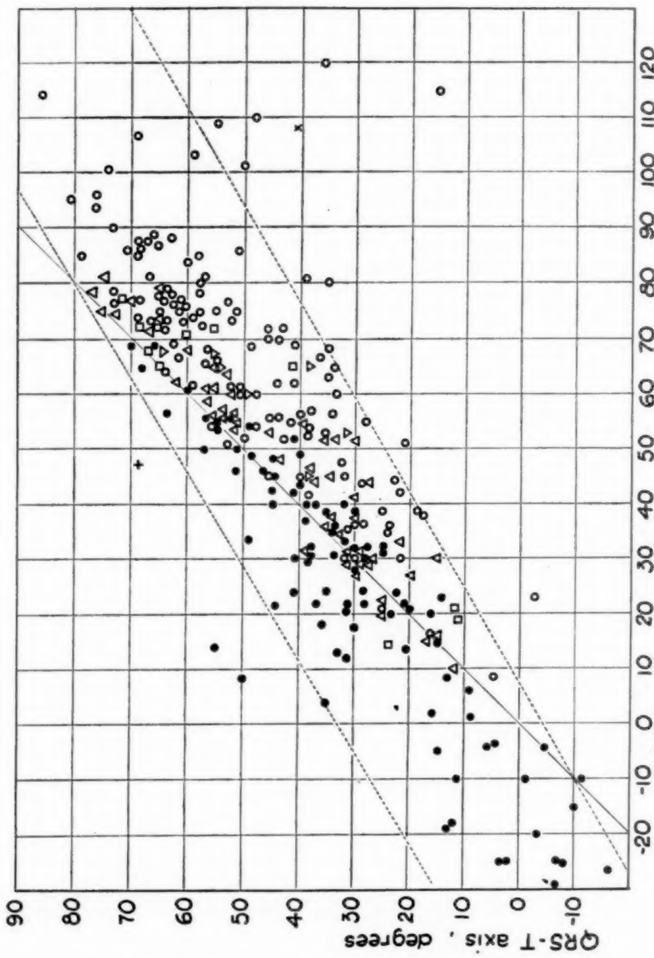

Fig. 2.—The relation between the mean axis of the QRS complex and the direction of the gradient, or the mean axis of QRS-T. As evidenced by the form of the QRS complexes, the hearts corresponding to the open circles were rotated clockwise; to solid circles, counterclockwise; to Δ, no rotation. For meaning of the other points, see text.

In Fig. 2, the average QRS axes are plotted against the directions of the ventricular gradients. Each of the 122 points represented by an open circle is from a case in which the electrocardiogram indicated clockwise rotation. It will be observed that, when the QRS axis is above +60°, not one of the gradients lay farther to the right than the QRS axis of the same heart, and all but one lay to the left of the QRS axis. When the QRS axis is below +60°, a few of the gradients lie to the right, although a majority still lie to the left of the QRS axis. It may be stated that when the electrocardiogram of the normal heart shows clockwise rotation, unless this rotation is extreme, the ventricular gradient rarely lies more than 5° to the right or more than 35° to

the left of the mean QRS axis. Sinus tachycardia was present in the large majority of cases in which the gradients approached the 35° limit.

In contrast, the 87 points represented by solid circles are examples of counterclockwise rotation, according to our criteria. In these cases, the gradient rarely lies more than 32° to the right, or more than 10° to the left of the QRS axis.

More interesting are the fifty-three points indicated by a delta. These are electrocardiographic examples of little or no rotation. With only two exceptions, their gradients lie within a narrow band, ranging from 5° to the right, to 17° to the left, of the QRS axis. The narrow range of deviation between the gradient and the mean QRS axis, amounting to only 22°, is, we believe, of considerable significance, particularly when we recall that not all of these hearts can be regarded as being strictly nonrotated. This observation suggests that, with few exceptions, the gradient and the mean QRS axis bear a close relation to each other in normal hearts. Furthermore, this fact, together with the ranges for the rotated hearts, strongly suggests that the electrocardiographic criteria for rotation are fairly reliable, although more remains to be done in establishing the kind of rotation in certain electrocardiogram types. In unpublished studies, using a different approach, Dr. Manuel Gardberg and one of us arrived at precisely the latter conclusion. It must be repeated here that this conclusion is quite independent of the further question as to whether or not the directions of the axes, as recorded, are their true directions.

There remain on the chart eleven points indicated by squares, and seven indicated by inverted deltas. The squares represent records in which there was an S wave in all three leads, with little or no Q wave in any lead, and with R_2 higher than R_1. The distribution of the points suggests that these hearts are relatively unrotated, or slightly rotated in a clockwise direction, although another interpretation is possible. The inverted deltas represent electrocardiograms that showed a Q, and no S, in each of the three leads. The distribution of the points suggests clockwise rotation.

There are 9 points for hearts rotated in a clockwise fashion whose gradients lie much farther to the left of their QRS axes than 35°. The five instances with a QRS axis of more than 90° are electrocardiographic examples of extreme clockwise rotation. The significance of their position is taken up in the discussion.

In 1937, Ashman and Hidden[5] published a paper on rightward deviation of the T-wave axis as an index of myocardial disease. Rightward deviation of the T wave is, of course, usually associated with similar deviation of the ventricular gradient. It is interesting to find that the results of that study, which was purely empirical, agree well with the limits of deviation of the gradient relative to the QRS axis, as reported herein. In that study it was tacitly assumed that hypertrophy of the left ventricle, sufficient to rotate the T wave abnormally

to the right, signified disease. That point of view is debatable. In any event, such hypertrophy is not normal, and disease is potential, if not present. For reasons which will be taken up in the second paper of this series, abnormality of the gradient should prove a much more reliable and consistent indication of disease than the T-wave amplitude or direction.

Bayley, Holoubek and Baker[6] concluded, from measurements of the gradients of 100 normal hearts, that, in patients with normal QRS complexes, the gradient should not lie more than 24° to the right of the QRS axis, nor more than 35° to the left of it. We have extended the total range as given by them, but, at the same time, we have narrowed it by suggesting separate narrower ranges for hearts differently rotated on their long axes.

In a later paper we shall consider the effects of disease on the gradients and the means of making proper correlations between the gradient and the QRS axis. For the present it may simply be pointed out that nonrotated hearts have gradients which range only slightly to either side of the QRS axis; that the gradients of clockwise rotated hearts range farther to the left, and that there is some correlation between the electrocardiographic evidence of degree of rotation and degree of deviation between the two axes; and that the gradients of the counterclockwise rotated hearts range to the right of the gradients of nonrotated hearts.

It is important to note that the relation between the QRS axis and the gradient, as outlined above, is valid only for hearts in which there is no defect or anomaly in intraventricular conduction. When the mean QRS axis changes as a result of such factors, the gradient, providing there is no myocardial change, remains unaffected, both in magnitude and direction.

(c) ***Rotation of the Heart About Its Transverse Anatomic Axis.***—It is well known that the longitudinal anatomic axis of the heart not only points downward and to the left, but is also directed forward to a greater or lesser extent. In persons with short anteroposterior thoracic diameters, the heart must be relatively vertical. Such a heart may be regarded as one, the apex of which is swung downward or the base upward. When the anteroposterior diameter is large, the valve openings are likely to be farther behind the anterior chest wall; the apex can be regarded as having swung forward and upward. We have not yet made a systematic study of the effect of this rotation upon the electrocardiogram, but there is good reason to suppose, as we shall point out in the discussion, that such rotation has its effect in producing QRS vectors of different magnitudes and in causing unusual degrees of deviation between the QRS axis and the ventricular gradient.

(d) ***Posture.***—In eighteen of a series of twenty-three cases, nineteen of our own, and four from Scherf and Weissberg,[7] a change from recumbency to the standing position caused the QRS axis to deviate to

the right. In five cases there was either no change or a slight shift to the left. The ventricular gradient shifted to the right in eleven of the twenty-three cases, and to the left in twelve cases. Without exception, the size of the gradient was diminished. In ten cases the size of the QRS vector was increased and in thirteen cases it was diminished by standing.

(e) ***Heart Rate and the Direction of the Gradient.***—In too large a number of cases for it to be accidental, we have observed a leftward shift of the gradient, relative to the QRS axis, with sinus or supraventricular paroxysmal tachycardia. The reason for this shift is obscure, although it is correlated with depression of the S-T segment in Lead III, and it may be related to a change in cardiac position during systole. Its extent is not great, as a rule. The four points in Fig. 2 which represent QRS axes of less than 90°, and gradients well to the left of the QRS, are from persons with sinus tachycardia, except one, who had paroxysmal tachycardia. The majority of the persons with slightly lesser gradient deviation also had rapid hearts.

That it is not the tachycardia itself, but a change associated with tachycardia under some, but not under all, conditions that causes a leftward shift of the gradient was shown by a study of six persons to whom amyl nitrite was administered. The increase in heart rate averaged 35 beats a minute, and ranged from 23 to 55 beats. In one person the gradient appeared to swing 8° to the right, but this effect was illusory, and was clearly caused by slowing of the heart between the taking of Leads I and III. In three others, also, the direction was essentially unchanged. In the other two persons, an apparently significant change was clearly related to a change in respiratory level. Although the number of cases is small, it can be stated that acceleration of the heart brought about by amyl nitrite inhalation has little, if any effect upon gradient direction in recumbent, normal subjects.

5. DISCUSSION OF RESULTS

(a) ***The Significance of the Relation Between Rotation on the Heart's Long Axis and the Angle Between the QRS Axis and the Gradient.***—We have noted that the gradients of hearts which are rotated clockwise around an axis which is close to the long anatomic axis point to the right of the anatomic axis, but to the left of the QRS axis. On the other hand, when the heart is rotated counterclockwise the gradient points to the left of the longitudinal anatomic axis, but to the right of the QRS axis. These relationships are so consistent that they can mean only one thing, as reference to Fig. 3 will show. The longitudinal axis of rotation points somewhat forward, downward, and to the left, as anatomic considerations suggest. The gradient axis points less far forward. It lies behind the longitudinal axis of rotation. Hence, when there is clockwise rotation of the heart, the tip of the gradient swings to the right, and vice versa. The QRS axis, in turn, lies behind the

gradient, so that, on clockwise rotation of the heart, it points farther to the right than does the gradient, and, consequently, the gradient points to the left of the QRS axis. On counterclockwise rotation of the heart the reverse changes occur. The QRS axis swings farther to the left than the gradient, so that the latter now points to the right of the QRS axis. We have already given our criteria for rotation of the heart on its long axis. We have checked the criteria against a considerable number of roentgenograms and electrocardiograms in Master's very useful book[8] and by means of a few fluoroscopic examinations; the consistency of the relation is very good. A later paper will deal in detail with the relation of the electrical axes to the anatomic axis.

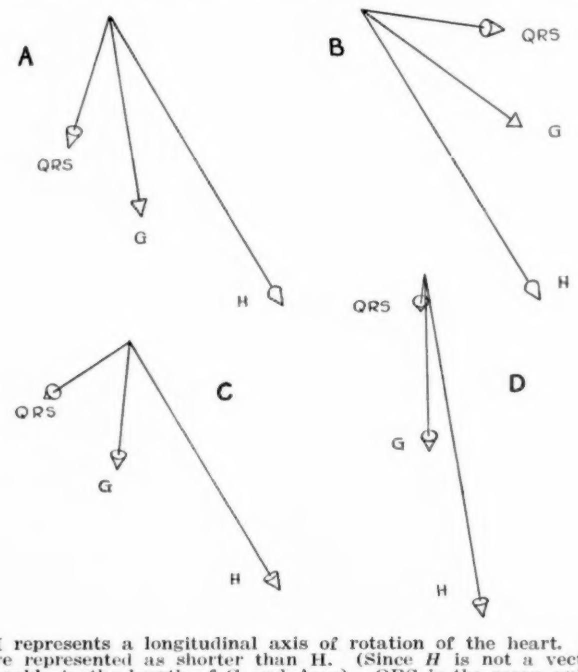

Fig. 3.—H represents a longitudinal axis of rotation of the heart. The G is the gradient, here represented as shorter than H. (Since *H* is not a vector, it has no length comparable to the length of G and A_{QRS}). QRS is the mean axis of the QRS complex ($S\hat{A}_{QRS}$), and in absolute length in our model (though not as projected) was about 85 per cent as long as SG.

The actual angle between H and G has not yet been accurately calculated. Therefore, the angle shown by the model, 35°, is merely for illustrative purposes.

The effect of changes in position, and of rotation about H, upon the angles can be mathematically ascertained. The diagrams, however, are taken from the shadow of the model, projected upon a white screen representing the frontal plane. The plane of the paper of this page is the frontal plane.

A represents a moderately vertical heart, rotated markedly in a clockwise direction (see text). The alpha angles of *G* and QRS correspond roughly to the point at the upper right corner of Fig. 2.

B is the same heart, rotated markedly counterclockwise. This approximates the first case discussed in section 5 c, although that heart was somewhat more transverse, and the rotation, though unusual for the heart position, not quite so great.

C shows the same heart, with the apex pushed back markedly. Note the effect upon the length of the vectors and upon the size of the angles. This position hardly ever occurs in normal chests.

D shows a very vertical heart, with only slight clockwise rotation; the apex is pushed back. The anatomic axis (not shown) still projects forward slightly. Foreshortening has greatly reduced the manifest area of QRS, but has less effect on the gradient, which lies in front of QRS. No point in Fig. 2 quite corresponds to this position. The QRS axis is at +100°, and the gradient at +90°.

(b) *The Size of the Angle Between the QRS Axis and the Gradient.*—This question will be considered in a later paper. Since rotation of the heart which we have designated clockwise or counterclockwise is about an axis which is possibly not identical with the longitudinal anatomic axis of the heart, the problem in question can be solved only after this axis of rotation has been considered. The rotation is not about the QRS axis, nor about the gradient. It can be said, however, that the angle between the QRS and QRS-T axis is approximately 25° to 35°, on the average.

(c) *Discussion of Exceptional Cases.*—We may anticipate the later report in order to discuss a few of the cases represented by points in Fig. 2. Reference to the diagrams in Fig. 3 shows that rather moderate rotation of the heart about a longitudinal axis will enable us to explain the rotations in the usual ranges, as they have been given. In two of the unusual cases fluoroscopic examination was done. One is shown twice in Fig. 2; the measurements from two separate electrocardiograms, taken at different times, are given. The points are those at a QRS axis of +4° and a QRS-T of +35°, and at +8° (QRS) and +50° (QRS-T). The person was a healthy medical student of sthenic habitus, tending toward hypersthenic, whose record showed the same peculiarities a year previously. His thorax was not abnormal in form and the heart was of normal size and in about the average position for his build. The pulmonary conus showed no prominence. Lateral and oblique views showed no peculiarities. His blood pressure was normal. His electrocardiogram, to be published in the second paper of this series, revealed a low T_1, a much higher T_3, and "left axis deviation." The waves R_1 and S_3 were of normal amplitude and the net manifest area of the QRS complex was 5.1 units (see section 1), in contrast with the average area for males of 6.7 units. There was, therefore, no electrocardiographic suggestion of hypertrophy. According to Ashman and Hidden's[5] work, the ratio T_1/T_3 was abnormal. Yet, to explain this unusual observation, all we need to assume is that the heart was rotated about 10° or 15° more in a counterclockwise direction than is common for a heart in this position. The angle between the QRS and the gradient for his second point (referred to in Fig. 2) is 42°. This angle is rather large, but may be explained either as the result of foreshortening caused by projection on the frontal plane, or to a real, although slight and unusual, deviation between the axes. On standing up, this subject's axes became 30° (QRS) and 43° (QRS-T), which is a common relation. A very slight change in the position of the heart can account for the differences in the two records which were taken in the supine position, but a 10 or 20° rotation clockwise around a long axis must be assumed to explain the difference between recumbency and standing.

The other atypical record from a patient who has been examined fluoroscopically is the point in Fig. 2 at +109° and +55°. In this case

the person was seated. As in the other case, we are indebted to Dr. James L. Gouaux for the fluoroscopic examination, which we witnessed. The person, employed by the hospital, is a healthy, young, colored woman of slender build. The anteroposterior diameter of her thorax is distinctly small, although there is no deformity. In the anteroposterior view the heart appeared somewhat enlarged, with a slight convexity of the pulmonary conus region, and not vertical. The angle between the horizontal and a line drawn from the angle between vena cava and auricle to apex was about 50°. Oblique and lateral views demonstrated that there was no actual cardiac enlargement. The net manifest area of the QRS complex was 3.1 units, in contrast with an average for women of 5.9. When the electrocardiogram was taken, the heart rate averaged 100/min. It showed rather marked "right axis deviation" and clockwise rotation. When, as in Fig. 2, we place the anatomic axis at 50°, push the apex back a few degrees to fit the flat chest, and rotate the heart clockwise, we quite readily reproduce the record as observed, except that the gradient is about 15° too far to the left. But since, when the heart rate is rapid, we often observe a shift of nearly this order of magnitude, we may say that the fluoroscopic observations quite satisfactorily fit the electrocardiogram. The QRS manifest area is small because of foreshortening of the QRS axis.

The point at +114° (QRS) and +86° (QRS-T) was from a rather slender, flat-chested medical student who was standing when the record was made. In the recumbent position, the axes were at +86.5° and +75°. The manifest area of the QRS was 7.6 in both positions. In spite of the relative flatness of the chest, the clockwise rotation of this subject's heart prevented marked foreshortening of the QRS axis. Hence, as projected on the frontal plane, the area of QRS was not small, and the angle between the QRS axis and gradient was not unusually large.

The point at 115° (QRS) and +15° (QRS-T) was from a tall, but heavy-set and rather obese, man, about 35 years of age. His blood pressure was variable, sometimes going as high as 190 mm. Hg, systolic. Hence, myocardial changes might be held responsible for the abnormalities, but they can be explained without that assumption. His heart rate was 115/min. Two other records, the last taken nineteen months later, showed no change. His electrocardiogram can be explained by assuming a very transverse heart, together with clockwise rotation, and a longitudinal axis of rotation which almost parallels the anterior chest wall. This assumption would necessitate a very small net area of the QRS, and, in fact, the area was only 1.4 units (the average is 6.7). We can assume that here we are dealing with a gradient which is greatly deviated by the tachycardia, but this can produce only a small part of the angle of 100° between the two axes. Perhaps the only unusual feature of this electrocardiogram is clockwise rotation, in the presence of a transverse heart.

The point marked X in Fig. 2 was from a case of pulmonary embolism. Both the QRS and T wave, and, therefore, the gradient, changes are those of marked clockwise rotation of the heart. It is obviously unnecessary to invoke any cause other than rotation and tachycardia to explain the more characteristic electrocardiographic changes which occur in this condition.

The point marked + is from a case, in the literature, of a middle-aged subject who had an attack of coronary thrombosis and died soon after the electrocardiogram was recorded. The record was interpreted as being quite normal. Actually, by the criteria of Ashman and Hidden, it was borderline. As a result of our present study we can say that the record was probably abnormal, for the QRS complexes revealed only a slight counterclockwise rotation and the heart rate was moderate. The first of our normal subjects, discussed above, revealed far more marked rotation.

Finally, three electrocardiograms were not included in the figure because their points fell far outside the range of the QRS axes shown. One, a 48-year-old man, was typical of the group. He had a QRS axis at −90° and a gradient at +66°. The manifest area of the QRS was 1.5 units, and, of the QRS-T, 8.5 units. There was an S wave, and no Q, in all three leads. S_1 had the same area as R_1, and S_3 was larger than R_3. Another subject, a slender medical student, complained of tachycardia. Examination revealed no evidence of heart disease. His QRS axis was −96°, and its manifest area, 2.3 units. His gradient was at +75° and was of normal size, taking into account the heart rate and small QRS area. On standing, his QRS shifted to −107°, and the gradient to +51°. He has suffered from bronchial asthma. Records such as these can also be explained but will be reserved for a later paper.

(b) *The Significance of the Distribution of the Points in Fig. 2.*—We have withheld a consideration of the peculiar distribution of the points in Fig. 2 until the discussion in the foregoing section could give the reader a general idea of the causes of the normal deviations between the QRS and QRS-T axes. It will be noted that the farther to the left the QRS axis lies, the less far is the gradient likely to lie to the left of the QRS axis. We interpret this simply to mean that relatively transverse hearts, for anatomic reasons, are not likely to be rotated far in a clockwise manner. Similarly, the farther to the right the QRS axis lies, the less likely is the gradient to lie to the right of the QRS axis. This evidently means that relatively vertical hearts, for anatomic reasons, are not often rotated much in a counterclockwise fashion. The dotted lines in Fig. 2 show the usual ranges, but points outside these ranges do not necessarily indicate disease.

6. APPLICATION TO ELECTROCARDIOGRAPHIC INTERPRETATION

In general, it may be said that a greater than normal deviation between the QRS and QRS-T axes, for the type and degree of longitudi-

nal rotation shown by the form of the QRS complexes, and not explainable as a result of foreshortening, or by a change in QRS size, as in bundle branch block or ventricular hypertrophy, is to be regarded as indicating myocardial change. It is true that the empirically arrived at criteria now in use are capable, in expert hands, of revealing disease in most instances, but a comparison of current texts shows quite clearly that uniformity in interpretation has by no means been achieved. The need for a more systematic and more rational procedure is obvious. The second paper in this series deals with the other aspect of the gradient, namely, its magnitude. When both the direction and magnitude of the gradient and their relation to the position of the heart in the thorax are considered, more accurate electrocardiographic interpretation should become possible.

SUMMARY AND CONCLUSIONS

The nature of the ventricular gradient is explained. It is the fundamental quantity in electrocardiography. Upon its magnitude and direction, in conjunction with the QRS vector, depend the size and direction of the T wave. Failure to appreciate this fact has tended to thwart efforts to define the normal and abnormal electrocardiogram by empirical methods.

A method of estimating the size and the direction of the QRS and QRS-T vectors is described.

The more important normal factors which determine the direction of the gradient, as projected on the frontal plane, are described and discussed; this was based on a detailed study of the electrocardiograms of 277 subjects, together with less detailed observation of over 200 other subjects.

The normal relation between the QRS-T and QRS vector directions is given and discussed.

A few exceptional individual cases are singled out for special discussion. These serve as an introduction to a later, detailed analysis of the relations between the electrical and anatomic axes, based upon roentgenographic, fluoroscopic, and electrocardiographic study.

Although the implications of our results are suggestive, our observations neither affirm nor deny the importance of tissues of variable electrical conductivity in contact with the heart. To prevent misunderstanding, we do not assert that the directions of the vectors as given in this and in the two following papers are their true directions in three-dimensional space. We do, however, believe that the evidence stresses the fundamental importance of vector analysis in the solution of electrocardiographic problems. We believe, further, that the method will go far to abate the existing chaos in electrocardiographic interpretation, a condition which a comparison of current texts so clearly reveals.

We wish to thank Dr. R. H. Bayley for a valuable critical review of the manuscript of this paper.

ON NOTATION

R. H. Bayley, M.D.

Unless a uniform system of notation is adopted, the presentation of material dealing with this important phase of electrocardiography will tend to confuse rather than help the reader. The following notation is therefore suggested:

Let the Einthoven triangle be replaced by its more convenient identity, namely, the triaxial reference system formed by translating the sides of the triangle in such a way that the midpoints of the sides coincide at a common point, the origin O (see Fig. 4). The lengths of the three references axes are immaterial, and the

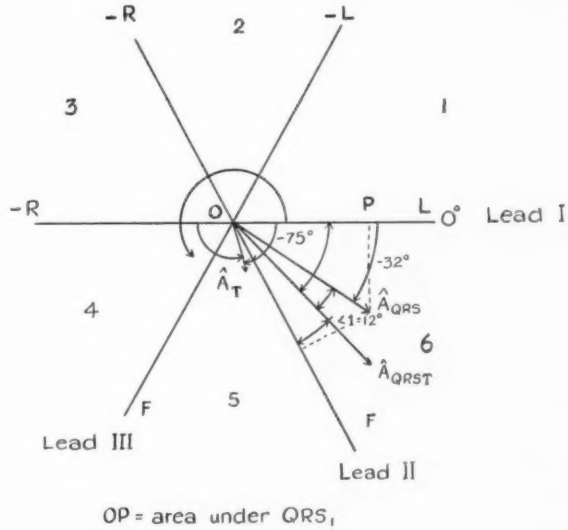

Fig. 4.

axes now divide the frontal plane, RLF, of the body into sextants. Each of the three reference axes, RL, RF, and LF, has a positive and negative half, separated by the origin O. Let the manifest mean axes be denoted as follows:

$\hat{A}_P$ = manifest mean axis of P,
$\hat{A}_{QRS}$ = manifest mean axis of QRS,
$\hat{A}_T$ = manifest mean axis of T,
$\hat{A}_{QRST}$ = manifest mean axis of QRST.

Here, the letter A indicates that the quantities are determined by the areas under the curves of the electrocardiographic deflections, and the arrowhead indicates that the quantities are vectors. Since the manifest mean axis of QRST is also known as the (ventricular) gradient, we have the identities $\hat{A}_{QRST}$ and $\hat{G}$. The motion of these axes is restricted to the frontal plane, RLF. The spacial mean axes, of which the aforesaid axes are projections, generally differ in both magnitude and direction from the manifest mean axes. Therefore, it is suggested that the spacial axes be denoted by prefixing the letter S to the foregoing symbols. Thus,

$S\hat{A}_P$ = spacial mean axis of P,
$S\hat{A}_{QRS}$ = spacial mean axis of QRS,
$S\hat{A}_T$ = spacial mean axis of T, and
$S\hat{G}$ = spacial mean axis of QRST or, spacial gradient.

Then, according to custom, the magnitudes of the axes (spacial and manifest) are SA_P, SA_{QRS}, SA_T, SG, and A_P, A_{QRS}, A_T, G, respectively.

The angle made by any two lines radiating outward from the origin O (which designates a common origin for all of the above mentioned vectors) is called a polar angle, and, according to custom, is indicated by writing in brackets the two lines by which the angle is formed. Thus, for the polar angle (1) in the figure, made by $\hat{A}_{QRS}$ and $\hat{A}_{QRST}$, we have the angle ($\hat{A}_{QRS}$, $\hat{A}_{QRST}$). In a like manner the polar angle made by $\hat{A}_T$ and the negative half of the Lead I reference axis (= –RL) is the angle ($\hat{A}_T$, –RL). A polar angle may be positive or negative; the sense is determined by the direction, counter-clockwise or clockwise, of measurement. When vectors or when polar angles are positive, it is customary to omit the positive sign. Thus, in the figure, the angle (RL, $\hat{A}_{QRST}$) = –45°, the angle (RL, –LF) = 60°, the angle ($\hat{A}_{QRS}$, $\hat{A}_{QRST}$) = –12°, the angle ($\hat{A}_{QRST}$, $\hat{A}_{QRS}$) = 12°, etc.

The positive reference axis of Lead I (= RL) is customarily taken as the general reference line from which all polar angles are measured, unless otherwise indicated (as in the aforecited instances). Thus $\hat{A}_{QRS}$ lies at –32°, and $\hat{A}_T$ lies at –75°, or at 285°, or, less specifically, in that half of the fifth sextant adjacent to the sixth.

The position of any of the spacial mean axes is not defined sufficiently by the position in RLF of the manifest mean axes. Hence, according to widely accepted standards for dealing with like situations, the polar angle made by a spacial mean axis and its related manifest mean axis is described as positive or negative according to whether the shortest motion through which the spacial axis appears rotated out of the frontal plane is counterclockwise or clockwise to an observer stationed at the patient's left. Thus, $S\hat{A}_{QRS}$ and $S\hat{G}$ (as described in the foregoing article) lie as if rotated through positive polar angles with respect to the frontal plane; the angle ($S\hat{A}_{QRS}$, $\hat{A}_{QRS}$) is greater than the angle ($S\hat{G}$, $\hat{G}$).

The magnitude of a manifest mean axis is always equal to the product of the magnitude of its related spacial mean axis by the cosine of the angle made by the spacial mean axis and its projection upon the frontal plane. For example,

$$G = SG \cos(S\hat{G}, \hat{G}).$$

In a like manner, the areas under the curve of the extremity lead electrocardiograms are always equal to the product of the magnitude of the related mean axis (spacial or manifest) by the cosine of the angle made by the limb of the triaxial reference system on which the area is plotted and the magnitude of the mean axis considered. For example,

$$\text{Area } QRS_1 = A_{QRS} \cos(\pm RL, \hat{A}_{QRS}).$$

Using the notation herein suggested, the manifest mean axes have the important relation,

$$\hat{G} = \hat{A}_{QRS} + \hat{A}_T,$$

or

$$\hat{A}_T = -\hat{A}_{QRS} + \hat{G},$$

where the vectors on the right-hand side of these expressions are added by the parallelogram law of adding forces. The negative sign before the vector quantity merely indicates a reversed direction in space, Thus, $\hat{A}_T$ is the directed diagonal (outward from O) of a parallelogram of which $-\hat{A}_{QRS}$ and $\hat{G}$ form two sides.

Finally, the axis of cardiac rotation, $\hat{R}$, with origin at O, usually makes a negative polar angle with respect to RLF. When it is desired to describe the position of $S\hat{A}_{QRS}$ and $S\hat{G}$ with respect to $\hat{R}$, the normal positions (according to the foregoing article) are such that the polar angles ($\hat{R}$, $S\hat{A}_{QRS}$) and ($\hat{R}$, $S\hat{G}$) are both positive with respect to $\hat{R}$, as viewed by an observer stationed at the patient's left. In the frontal plane, left axis deviation becomes positive mean axis rotation, and right axis deviation becomes negative mean axis rotation. When a mean axis deviates away from the normal in both magnitude and direction, the deviation may be referred to as a diversion. When a mean axis deviates towards its normal

value of magnitude and direction, the deviation may be referred to as a reversion. If a mean axis alters its magnitude without changing its direction, the alteration may be referred to as a growth or a decay, according to whether the magnitude increases or decreases.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

II. Factors Which Affect Its Manifest Area and Its Relationship to the Manifest Area of the QRS Complex

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IN THE preceding paper of this series[1] we gave an explanation of the way in which the ventricular gradient of Wilson, Macleod, and Barker[2] is estimated, with respect both to its manifest magnitude and direction, without, of course, giving its fundamental cause, for that is still unknown. We considered in some detail the relationship between the directions of the ventricular gradient and the QRS axis, and certain of the factors which affect that relationship. The influences which modify the magnitude of the gradient were considered in that paper only to the extent that was necessary to explain the magnitude of the angle lying between the two axes. This paper deals with the factors which affect the manifest area or magnitude of the gradient, and, incidentally, the size of the QRS vector. Of necessity, therefore, it deals with the factors which affect the magnitude and direction of the T wave of the electrocardiogram.

In order to avoid cumbersome verbal repetition, we shall employ certain of the symbols suggested by Dr. R. H. Bayley in his Appendix to the preceding paper. Because certain other symbols or usages are so firmly established, and a complete change would lead to confusion, we have not adopted Dr. Bayley's suggestions in toto. The symbols adopted are the following:

G is the manifest area of the gradient, as projected upon the frontal plane.

$\hat{G}$ is the gradient, considered as a vector, which has both magnitude (namely, manifest area) and direction, as projected upon the frontal plane.

A_{QRS} is the manifest net area of the QRS complex, as projected upon the frontal plane.

$\hat{A}_{QRS}$ is the QRS vector, and refers to both the magnitude and direction of QRS as projected upon the frontal plane.

The letter S, when placed before any of these symbols, makes the whole symbol refer to the true or absolute manifest area and/or direction of the vector in three-dimensional space, and not as it is projected upon the frontal plane.

All areas or magnitudes are expressed in units; each unit is one small rectangle of the electrocardiogram, or four microvolt-seconds.

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1. THE RELATIONSHIP BETWEEN THE VENTRICULAR GRADIENT, THE QRS COMPLEX, AND THE T WAVE OF THE ELECTROCARDIOGRAM

The relationship between these aspects or features of the electrocardiogram has been discussed by Wilson, Macleod, and Barker.[2] In the briefest possible manner we shall attempt to make this relationship clear by means of a concrete example. Let us take any human electrocardiogram and estimate the net QRS area and the net T area in Lead I and also in Lead III. Let us suppose that the net QRS area in Lead I is +5 units (20 microvolt-seconds), and that the net T (including any normal S-T segment shift) area in this lead is also +5 units. The + signs indicate that the larger deflection of the QRS and of the T is upright, or above the base line of the record. In Lead III, we may assume that measurement gives us precisely the same figures. In this case, then, the electrical axis, by Einthoven's triangle, of both the QRS complex and the T wave would be +60°. The gradient is obtained by taking the algebraic sum of the net areas of the QRS and T in each lead. These QRS-T sums are +10 in Lead I and +10 in Lead III. The direction of the gradient, as projected upon the frontal plane, is also +60° in this example, and its magnitude is obtained from the values in the two leads, as explained in the preceding paper. Here, its value is 20 units, or 80 microvolt-seconds.

Now we may accelerate this heart by administering amyl nitrite, and reduce the size of the T waves to half their former values. We shall assume that no change occurs in the size of the QRS complexes. The net QRS-T area in both leads, since the T waves are cut in half, is now +7.5 units. The direction of the gradient is still +60°, however. Although the gradient was reduced only 25 per cent, from 20 units to 15, the T-wave size is reduced by 50 per cent. With greater cardiac acceleration, the T waves may become low and diphasic, or isoelectric, and possess no net areas. The areas of QRS-T in both leads will now be +5 units, the gradient will lie at +60°, as before, and its size will be 10. Further cardiac acceleration may invert the T waves, so that the area in each of the two leads becomes −2.5 units. The algebraic sums, +5.0 and −2.5, are now +2.5 units in each of the two leads (in Lead II, of course, it would be +5.0 in this case); the gradient direction remains at +60°, and its size is 5 units. As a final step, let the gradient disappear. The T waves in all leads are now opposite the QRS complexes in average direction, and equal to the QRS complexes in area. Digitalis often has substantially this effect.

Of course, as was shown in the preceding paper, the directions of the QRS axis and of the gradient are not usually identical, even as projected on the frontal plane, and probably they are rarely identical in the normal heart, since normally an angle of about 30° separates the mean QRS axis ($\hat{SA}_{QRS}$) from the gradient ($\hat{SG}$), as these are located in three-dimensional space.

Local changes in the condition of the myocardium may change the direction of the gradient, and these may bring about abnormal changes in the T waves. For example, we may have net QRS areas like those in the example chosen, and the net area of the T wave in Lead I may also be +5 units. In Lead III, however, the net area of an inverted T wave may be −5, instead of +5 as in the first example. The figures from which gradient direction and size (G) are ascertained become +10 in Lead I, as before, but 0 in Lead III. The direction of the gradient is, therefore, +30°, and its size is 11.5 units. A simple method of ascertaining magnitude is given in the preceding paper. The QRS axis still lies at +60°.

Both the mean QRS axis ($\hat{A}_{QRS}$) and the gradient ($\hat{G}$) are vectors, for they have magnitude and direction. Given the magnitude and

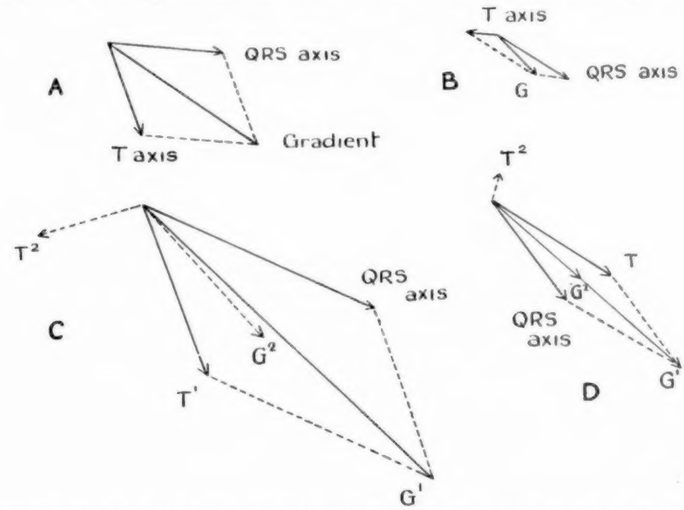

Fig. 1.—In *A*, the mean QRS axis ($\hat{A}_{QRS}$) is shown pointing to the left, forming an angle (angle α of Einthoven) of about 5° with the horizontal, or the line of Lead I. The heart is rotated in a counterclockwise direction around a longitudinal axis, which is not illustrated. Consequently the gradient, G, as explained in the preceding paper, points to the right of A_{QRS}. Since the gradient, G, is the algebraic sum of the net areas of QRS and T, its manifest magnitude and direction, as projected on the frontal plane, as R. H. Bayley has shown, can be derived from the QRS and T vectors by a construction giving, as in elementary physics, the resultant of two forces. This parallelogram of forces can obviously also be employed to find any one of the three vectors if the other two are known. In this example, taken from a healthy, recumbent, medical student, the manifest area of QRS ($\hat{A}_{QRS}$) was 5 units, and, of G, 8 units.

Upon standing (*B*), because of rotation of the heart, mainly upon its long axis, A_{QRS} shrank to 3.5 units and its direction became +30°. At the same time, the direction of the gradient changed slightly, but it was reduced in manifest magnitude from 8.0 units to 2.3 units. As a consequence, as *B* of this figure shows, the T-wave axis now pointed to the right, and became inverted in Lead I. The electrocardiogram is shown in Fig. 4.

C shows the axes from a hypertensive patient. Her first record showed the axes labelled QRS, G^1, and T^1. Since they are drawn to scale, it can be seen that they are much larger than in the normal subject, although A_{QRS} is still within possible normal limits, and G is not large. Three days later, with considerable acceleration of the heart rate, but while still recumbent, $\hat{A}_{QRS}$ was unchanged, but the gradient, G, and the T axis have shifted to G^2 and T^2, respectively. The T wave in Lead I is now sharply inverted. The electrocardiogram is shown in Fig. 5.

The T-wave changes in both cases are in reality caused by changes in the gradient. The axis of the T wave is forced to change when the gradient changes in magnitude, as the parallelograms show.

D simply represents a more usual picture with clockwise rotation. A decrease in G in such a case will bring about the typical decrease in the T waves which occurs upon changing from the supine to the standing posture, often with inversion of T_3, and even of T_2, as shown by G^2 and T^2. Case 20, in Table III, and the electrocardiogram of Fig. 6 illustrate such an effect.

direction of $\hat{A}_{QRS}$ and the mean T-wave axis, the direction and relative magnitude of the gradient, as projected upon the frontal plane, can easily be obtained by construction, as shown in Fig. 1. Or, conversely, given any two vectors, the other may be ascertained.

2. THE MATERIAL USED

The materials employed were the same as those used in the preceding study, except that, in the construction of the figures, data on sitting or standing subjects were excluded. Sixty additional electrocardiograms from patients without heart disease have been added, bringing the total to 270. All patients, even those without heart disease, were excluded if thyrotoxicosis or fever was present, for these affect the size of the gradient.

3. THE AVERAGE MAGNITUDE OF THE MANIFEST VENTRICULAR GRADIENT ($\hat{G}$) AND MANIFEST MEAN QRS AXIS ($\hat{A}_{QRS}$)

In normal persons, mainly below the age of 50 years, the average magnitude of G is about 13.0 units. The gradients of men are slightly larger than those of women. This is the explanation of the reported difference in the height of the T waves of men and women. However, when the sex difference in heart rate is allowed for, this difference in the size of the gradient becomes less, although it is still present. Tachycardia is much more common in women, and bradycardia in men. Of fifty subjects with heart rates of 60 or less in our series, nine were women. Of forty-one subjects with heart rates of 100 or more, only nine were men (Fig. 2.)

In contrast to the effect of heart rate on the size of the gradient, as discussed later, is its effect on the magnitude of $\hat{A}_{QRS}$. We are convinced, from a study of the rapid and slow hearts of the same subjects, that cardiac acceleration slightly reduces the net area of the QRS complexes. But this relation does not appear when the QRS areas of different persons are plotted against heart rate. This does not mean that there is no effect, but that it is masked by the other factors which cause far greater changes. There is, however, a sex difference in the size of QRS which is not dependent upon heart rate. In women this magnitude averages 5.9 units; and in men it averages 6.7 units. On the whole, therefore, at ordinary heart rates, G (13.0 units) is just about double A_{QRS} (6.3 units). Nearly 100 subjects were averaged in each group, so that the differences are statistically reliable within about ± 0.2 unit. In an earlier unpublished study, the QRS complex of women was found to be shorter than that of men, on the average. Since the units of QRS magnitude are time-potential units, a shorter duration, if the voltages are the same, would mean a smaller area, and, in this sense, the magnitude is related to the smaller average size of women's hearts. However, this is not necessarily the only reason for the difference.

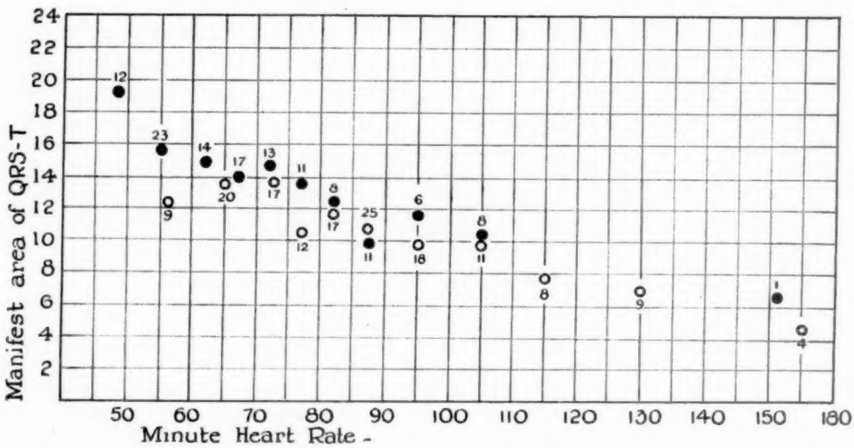

Fig. 2.—The relation between heart rate and the manifest area of QRS-T. Each figure indicates the number of subjects, the magnitudes of whose gradients were averaged to obtain the point on the graph.

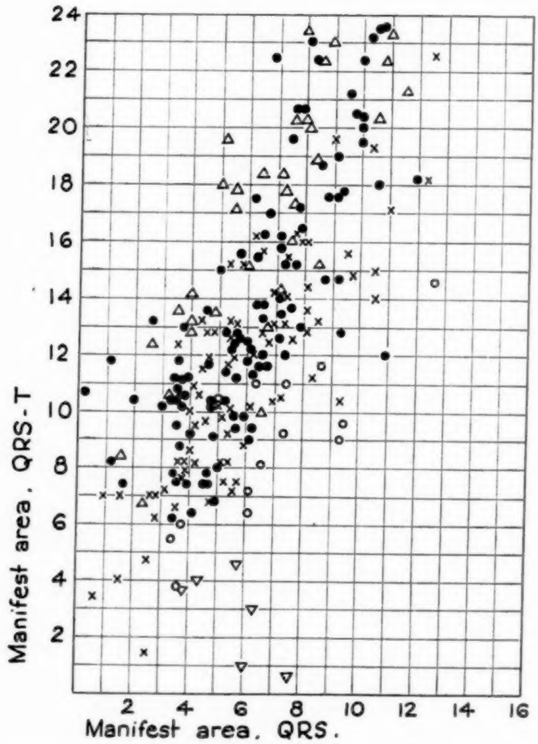

Fig. 3.—The relation between the manifest areas of QRS (A_{QRS}) and of QRS-T (G). Each point represents one subject. Deltas are from subjects whose heart rates ranged from 40 to 59/min.; solid circles, from 60 to 79/min.; X's, from 80 to 99/min.; open circles, 110 to 119/min., and inverted deltas, from 160 to 200/min. All subjects recumbent.

4. THE RELATIONSHIP OF HEART RATE, POSTURE, AND OTHER FACTORS TO THE MAGNITUDE OF THE MANIFEST VENTRICULAR GRADIENT

(a) *A Comparison of Different Subjects.*—As the heart rate increases there is a progressive and apparently almost proportional fall in G. This is shown in Fig. 2. Since factors other than heart rate have a marked effect upon G, the range in G among different subjects at each heart rate is very great. For this reason, only the average manifest area (G) for men and women is shown in the figure. The numbers beside each point indicate the number of individual cases which were averaged to obtain the value shown. As nearly as can be judged from the data, there is practically a straight line relationship between heart rate and G. At every rate but one on the curve it will be observed that the average value of G for men is slightly higher than that for women. If the gradient size were plotted against the cycle lengths, a curve would be obtained, with its concavity upward, which might be fitted fairly closely to an exponential formula, but much larger numbers of cases would be required to demonstrate a valid relationship. Examination of all of the data, only part of which is given in Fig. 3, shows that most of the very slow hearts had large values for A_{QRS}. As will be shown in the next section, this is the reason why the point graphed for the twelve men in Fig. 2 appears to be out of line with the others. If a correction factor for A_{QRS} (manifest area of QRS) were applied in each case, in accordance with the relationship shown in Fig. 3, and the relationship between G and heart rate were then plotted, a smoother curve would probably be obtained. Observation indicates that the range in the size of the gradient at each heart rate would be somewhat reduced.

As explained in the first section, the effect of heart rate in reducing the size of the T wave is greater than its effect on the magnitude of the gradient (G).

(b) *Amyl Nitrite.*—Amyl nitrite was administered to six male medical students. The resulting increases in heart rate, decreases in size of gradient, and changes in the manifest mean area of the QRS (A_{QRS}) are shown in Table I.

TABLE I

EFFECT OF AMYL NITRITE

SUBJECT NO.	INCREASE IN HEART RATE, %	A_{QRS} BEFORE AMYL N., IN UNITS	A_{QRS} AFTER	% CHANGE	G BEFORE AMYL N., IN UNITS	G AFTER AMYL N., IN UNITS	% DECREASE
1	32	8.1	7.4	− 8.6	14.4	11.0	23
2	33	9.3	9.3	0	10.7	8.9	15
3	34	3.6	3.8	+ 6.0	9.5	6.4	33
4	54	3.5	4.2	+20.0	10.3	7.6	25
5	57	5.1	4.0	−22.0	8.4	2.9	65
6	64	6.5	5.9	− 9.2	16.0	6.3	61

It will be observed, from comparison of the second and last columns, that there is a very rough correlation between the percentage of decrease in the magnitude of the gradient and the percentage of increase in the heart rate. It must not be forgotten that G, as recorded, is the magnitude of $\hat{G}$, the projection of $S\hat{G}$ upon the frontal plane. As may be seen from inspection of the third figure of our first paper, under most, although not under all, circumstances, a movement of the heart which results in a change, either an increase or a decrease, in A_{QRS} will be associated with a change in the same sense, although not of the same degree, in G. In three of these subjects, changes, presumably in respiratory level, caused definite alterations in the direction of $\hat{A}_{QRS}$. These were subjects 3, 4, and 5. In the other three, changes of this kind were negligible. Associated with the change in direction of $S\hat{A}_{QRS}$ (see introduction) was a change in A_{QRS}, which is the magnitude as projected on the frontal plane. This effect was most marked in subjects 4 and 5. In subjects 1 and 6, the slight, although measurable, shrinkage or decay in A_{QRS} was, we believe, mainly an effect of the increased heart rate. In subject 4, particularly, the rate effect was more than offset by the change in direction of $S\hat{A}_{QRS}$. The change in direction, therefore, both increased A_{QRS} in this case and also opposed the shrinkage in G due to an increase in heart rate. Hence, the apparent decrease in the latter is much less than the absolute decrease, namely, the decrease in $S\hat{G}$. In case 5, A_{QRS} decreased because of a change in the position of the heart, and the same effect, acting on G, reduced it more than it would have been reduced by the rate change alone. Case 2 is slightly out of line, and the reason was that a slowing in heart rate from 120 to 100/min. occurred after amyl nitrite between the taking of Leads I and III; this slowing was greater than in the other cases.

We may estimate that, on the average, a 50 per cent increase in heart rate brings about a 39 per cent reduction in gradient magnitude. Fig. 2 shows that men whose average heart rate was 111 had gradients which averaged about 32 per cent smaller than men with heart rates of 74, i.e., 50 per cent lower rates, with the percentage based on the latter figure. The order of magnitude of the effects of induced and spontaneous rate change are, therefore, in fair agreement.

As stated in the preceding paper, amyl nitrite produced no measurable direct effect upon the directions of the vectors.

The effects on the gradient of a change in the position of the heart will be the subject of our third paper. Much additional evidence for the correctness of our interpretations will be found in that paper. If the examples cited above had been isolated instances of the phenomenon in question, we would not have discussed them.

(c) *The Valsalva Experiment.*—Observations were also made on seven subjects, using the Valsalva maneuver to accelerate the heart. The recumbent subject inhaled and then blew against the fluid in a water

manometer, maintaining the level at ten or fifteen inches H_2O pressure for twenty seconds. Because of the changing respiratory levels, the results are not as satisfactory as those obtained with amyl nitrite, but they show just as clearly the decrease in the magnitude of the gradient. In three subjects, the gradient reverted to normal size within three or four beats after the beginning of the reflex slowing of the heart which followed release of air from the lungs. In one subject, 50 years old, with marked reflex slowing, the gradient was reduced still further for the first beat or two at the low rate. In three subjects, a slight, but measurable increase in G appeared during the period of slower beating, and in one of these the slowing was very slight. With the beginning of the Valsalva experiment the changes are progressive, and apparently keep pace with the acceleration of the heart. Immediately after the release of air there are about five beats, often with further rate acceleration, before reflex slowing begins. These beats sometimes show an apparent gradient increase, and sometimes a decrease, but the results are doubtful because of the shift in respiratory level and the unknown effect on the electrical fields of excess air in the lungs.

(d) *Muscular Exercise.*—The effect of exercise upon A_{QRS} and G was studied in six subjects, two of whom were used twice, with different procedures. In four experiments the subjects were seated on a stationary bicycle, and the records were taken before, and at short intervals beginning immediately after, exercise. Unfortunately the ergometer was not in operation, so that a measure of the work done was not obtained, but it was relatively small. In four other experiments the subjects were recumbent when the records were taken, and the exercise, more severe in three cases, was standing running with simultaneous arm movements. To this group we have also added an excellent illustration from a recent paper by Twiss and Sokolow,[3] and have studied the example published by Barker, Schrader, and Ranzoni,[4] in which the exercise was more strenuous.

The results are given in Table II. In the seated subjects, who exercised relatively lightly, there was an apparent relation between the percentage increase in heart rate and percentage decrease in G. Since the changes in the QRS magnitude were negligibly small, no adjustment of the effects is necessary. In three recumbent subjects the manifest mean QRS area was reduced, and by about the same amount; in one it was increased; and in one there was no change, which is equivalent to a relative increase, for the dromotropic effect of the sympathetic should slightly reduce A_{QRS}. When the effect of exercise on the supine subjects is compared with the effect of amyl nitrite, it is evident that the decrease in G is relatively small in proportion to the increase in heart rate; and when correction is made for the decrease in A_{QRS}, the difference becomes even more striking. When Barker, Schrader, and Ranzoni's[4] cases are examined, this fact becomes yet more evident. In their experiment, in spite of the severe exercise, and, in the unpub-

TABLE II

EFFECT OF EXERCISE

SUBJECT	% INCREASE IN HEART RATE	A_{QRS} BEFORE EXERCISE	A_{QRS} AFTER EXERCISE	% CHANGE	G SIZE BEFORE EXERCISE	G SIZE AFTER EXERCISE	% DECREASE
				Sitting			
1	10	6.6	6.6	0	12.0	10.6	12
2	31	9.3	9.0	−3	14.2	10.7	25
3	31	5.9	5.8	−2	12.9	9.9	23
4	39	7.6	7.4	−3	12.4	7.3	41
				Recumbent			
5	12	3.6	4.1	+14	9.5	8.2	13
2	28	11.6	9.9	−15	18.5	11.1	41
4	55	9.2	8.2	−11	16.2	11.2	31
6	56	7.2	7.2	0	15.4	13.4	13
T & S	83	5.1	4.4	−14	17.2	12.5	27

lished record, in spite of the great increase in heart rate, the T waves were actually increased in amplitude immediately after exercise, although, as the heart slowed, they became reduced. This increase in the height of the T wave does not mean an increase in G, because the waves were much narrower, but it is at least evident that the increased rate during severe exercise produces a far smaller reduction in G than the same rates during sinus tachycardia at rest or after amyl nitrite. In this respect, severe exercise is like fever or thyrotoxicosis.

In our experiments no increase in the height of the T wave was observed.

(e) *Change in Posture.*—In studying the effect of a change from the supine to the standing posture, we made use of four electrocardiograms published by Scherf and Weissberg[5] (in their Fig. 5 we interchanged Leads III in *b* and *c*, on the assumption that they were reversed), and added 20 cases of our own. We found that the effects of standing, given in Table III, were precisely like those described by Scherf and Weissberg, and by others.

To increase muscular relaxation, our standing subjects leaned against a wall. Without exception, G was reduced in the standing, as compared with the supine, position. We are in complete accord with Scherf and Weissberg's[5] statements that the change is not entirely dependent upon heart rate changes. The form of the QRS complex suggested very slight clockwise rotation on standing in about half the cases, and no appreciable change in most of the others. In two or three cases, however, very slight counterclockwise rotation around the heart's longitudinal axis of rotation was indicated. In most of the cases in which the mean QRS axis ($\hat{A}_{QRS}$) deviated to the right on standing, the gradient also deviated to the right, but the extent of the deviation of $\hat{G}$ was less than that of $\hat{A}_{QRS}$. On the other hand, when $\hat{A}_{QRS}$ deviated to the left, the leftward shift of $\hat{G}$ was usually greater than the deviation of $\hat{A}_{QRS}$ (Cases 3, 10, 14, 23). This means that, in

TABLE III

EFFECT OF CHANGE FROM SUPINE TO STANDING POSTURE

SUBJECT	BODY BUILD	% INCREASE IN HEART RATE	A_{QRS} SUPINE	A_{QRS} STANDING	% CHANGE	G SUPINE	G STANDING	% DECREASE	CHANGE IN QRS AXIS (F)	CHANGE IN QRS-T AXIS (F)
1	Hypersthenic	40	3.6	4.7	+31	9.5	6.7	30	+12°	+ 9°
2 (a)	Hypersthenic	22	5.5	5.0	– 9	7.1	3.8	46	+22°	+12°
3	Hypersthenic	26	7.7	8.5	+ 9	12.1	9.5	21	– 2°	–10°
4	Tall, hypersthenic	43	9.5	8.5	–11	21.0	13.8	34	0	– 3°
5	Hypersthenic	7	5.6	7.9	+41	9.2	8.5	8	+ 9°	+14°
6	Short, sthenic	25	3.5	4.0	+14	10.3	7.4	28	+42°	+ 9°
7 (d)	Sthenic	34	5.0	3.5	–30	8.0	2.3	71	+26°	+ 8°
8	Short, sthenic	6	5.1	4.9	– 4	11.0	9.0	18	– 2°	– 1°
9	Short, slender	31	6.5	5.1	–22	16.0	13.5	16	+14°	+12°
10	Short, sthenic	6	7.4	5.7	–23	14.0	10.4	26	– 6°	–10°
11	Slender	43	7.6	7.5	– 1	16.2	6.8	58	+27°	+11°
12 (b)	Tall, slender	11	18.3	21.0	+15	15.2	12.3	19	+ 7°	+ 7°
13	Tall, sthenic, muscular	15	4.8	5.0	+ 4	12.4	9.4	24	+19°	+ 4°
14 (c)	Slender	17	–2.3	–3.5	+52	7.6	3.4	55	–11°	–24°
15	Sthenic	34	6.7	6.2	– 7	9.6	4.2	56	+10°	– 8°
16	Sthenic	16	4.9	5.7	+16	10.5	6.8	35	+21°	– 4°
17	Heavy, sthenic	17	1.6	0.8	–50	7.4	4.2	43	+23°	– 4°
18	Sthenic	14	10.8	9.3	–14	14.5	9.3	36	+ 3°	+ 2°
19 (d)	Slender to sthenic	13	4.9	4.7	– 4	7.0	5.1	27	+ 2°	– 4°
20 (e)	Sthenic	41	10.9	11.0	+ 1	12.0	2.0	83	+ 3°	+ 5°
21	From S & W, Fig. 1	0	9.7	9.0	– 8	14.8	10.0	32	+ 9°	+11°
22	From S & W, Fig. 2	20	5.3	6.2	+17	10.5	7.0	33	+ 7°	–13°
23	From S & W, Fig. 4	16	8.1	8.7	+ 7	8.7	4.2	52	– 1°	– 6°
24	From S & W, Fig. 5	31	8.1	8.4	+ 4	19.0	16.3	14	+ 3°	–11°

(a) The recumbent heart rate was 88, and this partly explains this subject's rather small gradient. Subject 5 had a supine rate of over 100.

(b) An example of the Wolff-Parkinson-White syndrome, which explains the large QRS areas.

(c) This subject's supine mean QRS axis was –96°, and changed to –107° on standing.

(d) More often than in patients, the normal subject's electrocardiogram was taken an hour or two after eating; this often reduces the gradient (Gardberg and Olsen[6]).

(e) Most of these subjects were medical students. Subject 20 was trained, and probably relaxed more on standing. In this case, G was difficult to measure accurately on standing because of its small net area.

(f) A plus sign means clockwise rotation around the A-P axis, that is, rotation to the right, and vice versa.

the majority of cases, $\hat{G}$ shifted to the left *relative* to $\hat{A}_{QRS}$; the average deviation was just 10°. Clockwise rotation of the heart on a longitudinal axis would produce this effect, but when $\hat{A}_{QRS}$ deviated to the left on standing, $\hat{G}$ should not have been deviated to the same extent if the effect is the result of rotation (section 5, preceding paper). We may conclude, therefore, that the increase in heart rate, as pointed out in our first paper, may be one factor associated with, or perhaps causing, the relative leftward deviation of $\hat{G}$. Clockwise rotation on the long axis is another factor. A third factor, associated with the standing posture itself, may possibly also have helped cause the relative leftward deviation of $\hat{G}$, but there is no direct evidence for the existence of such a factor.

The magnitude, A_{QRS}, increased about as often as it decreased, and sometimes the change was within the limits of error in measurement. There was no particular correlation between the changes in the magnitude, A_{QRS}, and the changes in direction of $\hat{A}_{QRS}$ or in cardiac rotation. Nevertheless, in every case, the observed changes are readily explained by assuming that, on standing, most hearts become slightly more vertical in the sense that the base moves a little farther from the spinal column and/or by assuming a slight cardiac rotation (in two or three cases it was more than slight), either clockwise or counterclockwise on a long axis. When the electrocardiogram indicated that clockwise cardiac rotation had occurred, clockwise rotation proved to be required to explain the changes, and usually vice versa. Our third paper will deal more fully with this aspect of the question.

Mayerson and Davis[7] have studied the effects of tilting table experiments upon the electrocardiogram. Their results were similar to ours and those of Scherf and Weissberg, although perhaps more exaggerated. In general, $\hat{A}_{QRS}$ deviated to the right when the subject was raised from the supine to a nearly vertical position; the gradients, as in our experiments, deviated either to the right or to the left, and were reduced in size. The authors emphasized the T-wave changes, which amounted to inversion of T_2 and T_3 in some cases, and were accompanied by depressions of S-T_2 and S-T_3 exceeding 1 mm. in several instances.

For the benefit of those who wish to see for themselves whether the relation between the change in $\hat{A}_{QRS}$ and $\hat{G}$ (described under amyl nitrite) applies to the results in the table, it is pointed out that, in subject 14, $\hat{A}_{QRS}$ shifted from -96° to -107°, and simultaneously increased in magnitude. Visualizing this in terms of the spatial axes, namely, $S\hat{A}_{QRS}$ and $S\hat{G}$ (Fig. 3 of the preceding paper), shows that, in this particular subject, G should get smaller, not larger, with the increase in QRS area. The very large decrease in this subject's gradient, associated with only a moderate increase in heart rate, agrees with this conclusion. In subject 17, although the percentage change in $\hat{A}_{QRS}$ was large, the absolute change was small. This must also be considered.

(f) *A Comparison of the Effects of Amyl Nitrite, Postural Change, and Exercise.*—Table IV shows the effects of amyl nitrite, postural change, and exercise upon the magnitude, G. In order to obtain a quantitative expression of the relative magnitude of the effects brought about by these factors, we have divided the average percentage decrease in G by the average percentage increase in heart rate. It will be seen that, in proportion to the increase in heart rate, postural change has a far greater effect than the other two procedures. Since there are twenty cases in this group and fifteen (with two subjects used twice) in the other two groups combined, the observed differences are undoubtedly significant. As explained above, our results also indicate that G is reduced more by amyl nitrite inhalation than by exercise, and this difference is the more striking when the supine, exercised subjects are considered. The difference did not appear in the seated, exercised subjects. After allowance is made for the changes in $\hat{A}_{QRS}$, the difference is still more obvious. Although the number of cases is small, our observations after exercise are, therefore, fully in accord with those of others, who have reported an actual increase in the height of the T waves during or immediately after exercise.

TABLE IV

A COMPARISON OF THE EFFECT OF AMYL NITRITE, EXERCISE, AND STANDING POSTURE ON G

PROCEDURE	NUMBER OF EXPERIMENTS	I AVERAGE PERCENTAGE INCREASE IN HEART RATE	II AVERAGE PERCENTAGE DECREASE IN GRADIENT SIZE	II/I
Amyl nitrite	6	45.7	36.2	0.79
Exercise, sitting	4	27.8	25.2	0.91
Exercise, supine	5	46.8	23.0	0.49
All exercise	9	38.3	24.0	0.61
Standing posture	20	23.0	36.5	1.59

(g) *Ingestion of Food.*—It was pointed out by Gardberg and Olsen[6] that the T wave became lower after meals in a majority, although not in all, normal subjects. The change began about an hour after eating and persisted for about two hours. The effect ranged from zero up to a 50 per cent reduction in T-wave height, which corresponds to approximately a 25 per cent decrease in gradient magnitude. The experiments were properly controlled and have been confirmed by us. We regard the possible effect of eating as the major uncontrolled variable in our present observations. Fortunately, the majority of the hospital electrocardiograms were taken in the forenoon.

4. THE RELATIONSHIP BETWEEN THE MANIFEST AREA OF QRS AND THE MANIFEST AREA OF QRS-T

According to the interpretation given in Fig. 3 of our previous paper, the net area of QRS in all limb leads may equal zero if, by chance, the

spatial QRS vector ($S\hat{A}_{QRS}$) points, or appears to point, straight backward at right angles to the frontal plane. We have encountered no electrocardiogram which gave a manifest QRS value of zero, but in several cases the areas were extremely small; in one the manifest area was only 0.2 units, and $\hat{A}_{QRS}$ was apparently $-60°$. This was a hospital patient, 47 years old. He had a history which was compatible with, although not quite typical of, angina pectoris. He complained of dyspnea at night; his blood pressure was 124/84, and there were no signs of heart failure. His electrocardiogram was interpreted as being normal. His heart rate was 64/min. when the record was taken; G was 10.7, which is slightly small for the heart rate, but perfectly normal, as we shall see, in proportion to his A_{QRS}. The direction of $\hat{G}$ was $+69.5°$. If we are right concerning the position of $S\hat{A}_{QRS}$, it is obvious that his A_{QRS} could hardly have become smaller on standing. In fact, it increased to 2.7, and its direction became approximately $-102°$. The gradient, on the other hand, decreased to 2.1 units, and its direction (not very reliable in this case) shifted to $+44°$. These changes are readily explained if we assume that, on standing, the cardiac apex tilted toward the left and backward *relative* to the base (or the base tilted to the right and forward) only a few degrees; and that, simultaneously, there was a very slight leftward shift of the gradient caused by the increase in heart rate from 64 to 75/min. or by the standing posture. Aside from the rather unusual character of the record, there was no electrocardiographic evidence of heart disease. The patient was not subjected to exercise.

We may now return to our main point. It should be clear from Fig. 3 of the first paper that when the area, A_{QRS}, is zero, the gradient, although foreshortened and relatively small, must still be of fair magnitude, as in the case just described. When the heart is in a more usual position, $S\hat{G}$, which now lies more nearly parallel to the frontal plane, should, on the average (due account being taken of posture and heart rate) be projected upon that plane as a larger G. G should achieve its maximum normal magnitude when the heart is in about the average position and rotated rather strongly in a clockwise fashion. In this position, also, A_{QRS} should approach its greatest normal magnitude. The facts, as far as they have been investigated, agree with these expectations, particularly with respect to the magnitude, A_{QRS}.[8] Somewhat more vertical, although not extremely vertical, hearts are also likely to have large gradients, and this is also in line with expectation. The third paper, which will include roentgenographic and fluoroscopic evidence, will treat this phase of our subject.

Fig. 3 shows the relationship between A_{QRS} and G in supine subjects. The solid circles are from subjects whose heart rates ranged from 60 to 79, inclusive. The patient discussed above, although doubtfully normal, is added on the figure. Although the vertical scattering of points on the graph is rather great, as might be expected, there is, nevertheless, a fair degree of correlation between the magnitudes of

the vectors. No useful purpose could be served by treating this correlation statistically, for too many influences, aside from heart rate and A_{QRS}, may affect the gradient. Yet, when heart rate is stabilized in the recumbent subject, under basal conditions, these other factors probably have less influence than might be supposed. The rate range 80 to 99 is shown by the points marked x; the range 40 to 59, by deltas; the range 110 to 119, by open circles, and the range 160 to 200, by the inverted deltas. To avoid further confusion of points, the ranges from 100 to 109 and from 120 to 159 were omitted, although they showed the same correlation. In general, however, the faster the rate, the poorer the correlation between A_{QRS} and G. This means, we believe, that not all the sinus tachycardias selected were a consequence of the same causes, whatever those causes may have been. As A_{QRS} increases beyond about 8.0 units, there is a tendency for the largest gradient values to reach a ceiling, so that, with further increase of A_{QRS}, further gradient growth cannot occur. And, as our study of abnormal hearts shows, the gradient probably shows no increase when A_{QRS} is increased by hypertrophy or intraventricular block beyond the limits shown in the figure (see Case 12, Table III).

Even though the scattering of points is great in Fig. 3, it does suggest that, at each heart rate and A_{QRS} value, there is a minimum value below which G is not likely to fall in normal hearts; and a few of the points may possibly be abnormally high. For rates between 60 and 79, for example, there seems to be a definite sloping level below which the points rarely fall, and there are 101 points in that rate range. By extrapolation, we may infer that the gradient would nearly disappear at a heart rate of about 240/min.

The largest values of G were shown by thirteen hearts, all of whose G values lay in the range of 23.0 ± 0.6 units. This apparent ceiling is probably a coincidence. No doubt an occasional gradient will go higher. The upper limit of the normal value for A_{QRS} may be placed at about 11.0 or 12.0, although three hearts in 270 seemingly had larger values. None was above 12.6 units. The lowest presumably normal A_{QRS} value observed by us was in Case 14 (Table III), but there was a history of bronchial asthma. Nothing unusual was seen in the fluoroscopic examination, other than a very vertical heart. A_{QRS} was -3.5 units when the subject, a medical student, was standing. Since the present paper was first drafted, another similar record was obtained from a young physician concerning whose freedom from cardiac or pulmonary disease there is no doubt.

It must be emphasized that the gradient values are for recumbent subjects. The values of A_{QRS} will apply to seated subjects as well.

5. DISCUSSION OF INDIVIDUAL CASES

The most interesting example of a change in G was shown by a man, a normal medical student, who was the first subject discussed in the preceding paper because of the peculiarity of the directions of his axes.

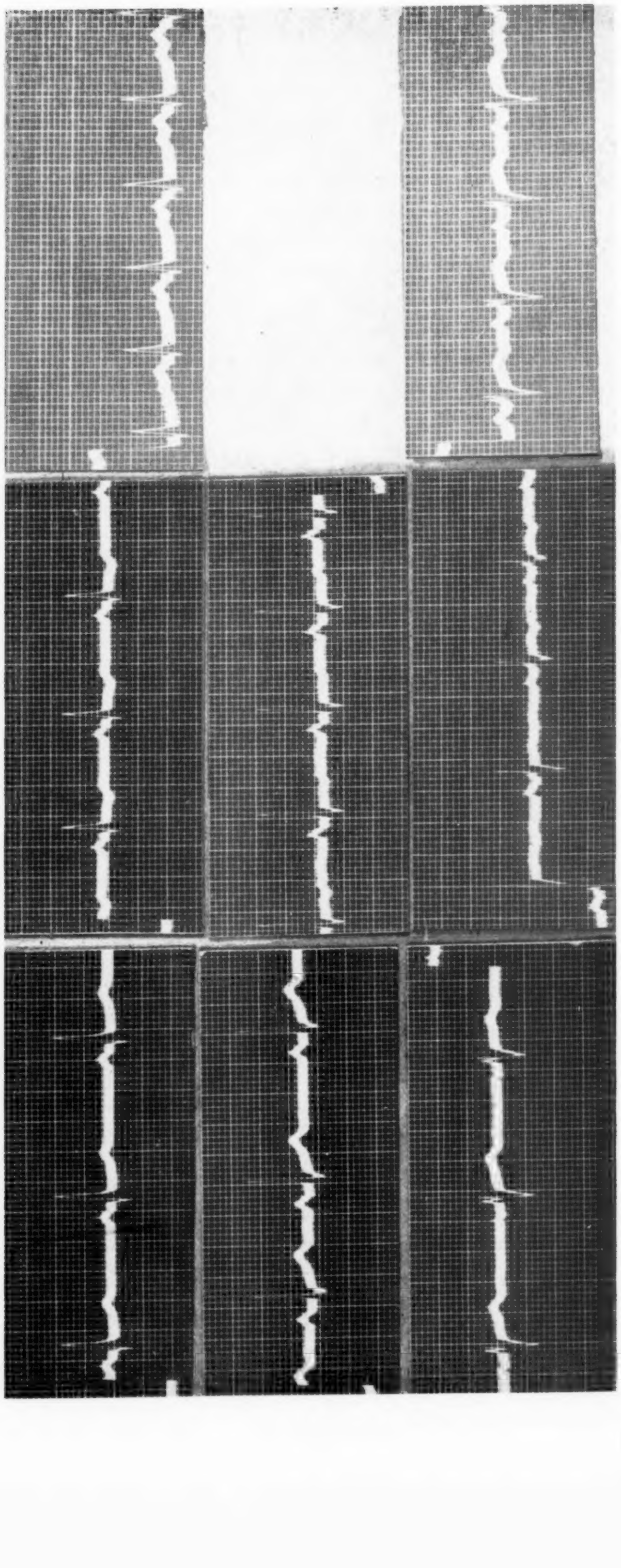

Fig. 4.—Electrocardiograms, before and after standing, from a healthy medical student, 23 years old. This is interpreted in the text and in Fig. 1; it is Case 7 in Table III.

When recumbent, his $\hat{A}_{QRS}$ was +4°, and its manifest area, 5.0 units. His gradient was at +35° and its manifest area was 8.0 units. Rather marked counterclockwise rotation of his heart was indicated by the form of his QRS complexes (Fig. 4). The degree of this cardiac rotation is unusual for a normal heart in a subject of sthenic habitus. Upon standing, $\hat{A}_{QRS}$ was +30°, and $\hat{G}$ was +43°. At the same time, A_{QRS} decreased to 3.5 and G diminished to 2.3 units. A very moderate shift in the position of the heart would suffice to bring about all these changes, except the marked reduction in G. Evidently, there was cardiac rotation in a clockwise direction, that is, lessened counterclockwise rotation, and this is also shown by the character of the QRS changes. The position of the heart may have become slightly more vertical, as well. Both vectors, $\hat{A}_{QRS}$ and $\hat{G}$, were shortened. S$\hat{G}$ was shortened absolutely, as is typical upon standing. Fig. 4 shows the effect of these changes upon the T waves. T_1 becomes inverted. In this subject, because of the slightly unusual cardiac rotation, the characteristically normal diminution of the gradient could produce no other electrocardiographic effect. After amyl nitrite (Fig. 4), the net T area was again rendered negative in Lead I by depression of the S-T segment, although the T wave proper, so-called, remained upright. Quite incidentally, this observation should demonstrate that not all S-T segment shifts mean coronary disease or even temporary ischemia, for a vasodilator drug was employed. This point was brought out by Scherf and Weissberg.[5] The changes in the form of the T waves which occur under these two conditions tend to show that the mechanism of the reduction in the size of the gradient brought about by the different procedures is not the same. Concerning this subject we can say, although not seriously, that standing produced digitalis-like changes, and amyl nitrite caused effects like those often ascribed to coronary insufficiency. It is evident that these differences deserve careful study, but investigation by the usual type of empirical observation may prove worse than useless.

Fig. 5*A* shows the electrocardiogram of a 32-year-old woman whose arterial blood pressure was estimated at 270/150. She also had a goiter, and had had no digitalis. The first electrocardiogram is fairly typical of long-standing hypertension and left ventricular hypertrophy. $\hat{A}_{QRS}$ was 11.0 units in magnitude and its direction was +23°. $\hat{G}$ was 17.2 units in magnitude, and its direction, +42°. The axis of QRS-T lay to the right of the QRS axis, as is typical of a heart which is rotated counterclockwise (see preceding paper). The heart rate was 92/min. in Lead I. Three days later the electrocardiogram shown in Fig. 5*G* was taken. The heart rate was 119/min. in Lead I. The QRS axis was unchanged at +23°, and the axis of QRS-T was +48°. The change is slight, and the fact that the rate was slower in Lead III than in Lead I may be the cause. But the manifest area of QRS-T decreased from 17.2 to 9.2. On both occasions the patient was recumbent. As shown in the diagram of Fig. 1, the inversion of T_1 in the second record was

almost wholly the result of the reduction in G, which, in turn, may be almost fully accounted for by the increase in heart rate. Unfortunately, another record was not obtained, with reversion to a slower cardiac rate. We feel, however, that a classification of pictures of "left ventricular strain" into various types which depend upon changes in such a labile abstraction as the T wave may be a precarious undertaking. However, when the cardiac rate is within usual limits, changes in G, and, consequently, changes in the T wave, may prove to be of clinical significance.

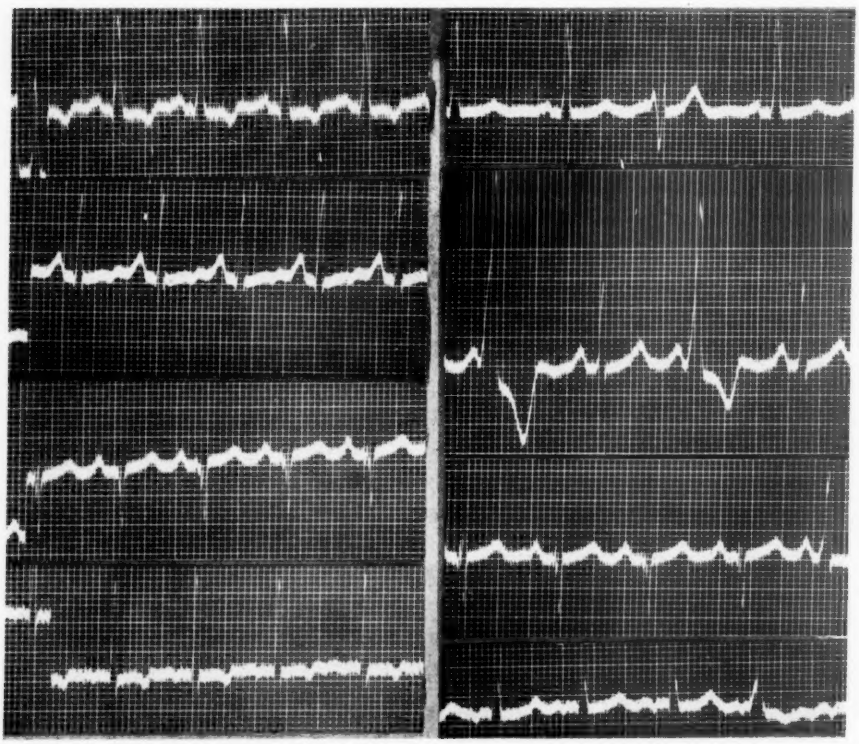

Fig. 5.—Electrocardiograms from a patient with hypertensive heart disease, before and after acceleration of the heart. Discussed in text and illustrated in Fig. 1.

6. DISCUSSION

The major problem which remains in electrocardiography is to discover the fundamental cause of the electrical forces which produce the ventricular gradient. The data presented in this paper and in the preceding one may assist us in solving the problem by indicating an appropriate type of animal experimentation. Even though this fundamental problem remains unsolved, it is, nevertheless, possible to attempt to explain the effect of one of the normal factors which reduces the magnitude of the gradient, namely, the effect of heart rate. It should be recalled that amyl nitrite, which is said to have little effect on the minute cardiac output,[9] reduces the size of the gradient. Since the

heart is accelerated, the output per beat is reduced, and this may be a factor. During strenuous exercise, on the other hand, the output is increased to a greater extent than the rate,[10] so that the output per beat is increased; yet the size of the gradient diminishes under the conditions of our experiments, but it may apparently be little reduced or even increased when the exertion is more severe.[4] The standing posture slightly reduces cardiac output, at least in many persons, and, even in the absence of rate change, output per beat and gradient magnitude are reduced. In unpublished experiments, Mayerson and Davis,[14] by means of the roentgenkymograph, observed a decrease in the size of the heart and a reduced stroke volume in their vertically placed subjects. A comparison of the several results indicates that at least two factors are concerned. One is the heart rate; the other may be the cardiac output per beat. Since all the procedures employed may be expected to bring about an augmentation of sympathetic tone, it is unlikely that this is an important factor in causing the *quantitatively* different effects, and Nordenfelt[11] has shown that the postural effects persist after administration of ergotamine tartrate.* That reflex constriction of the coronaries plays a part is highly improbable, for, in order to cause a significant restriction of the oxygen supply to the heart muscle, an unphysiologic degree of constriction would be required. This is discussed by Scherf and Weissberg.[5] Furthermore, it may safely be assumed that amyl nitrite causes coronary dilatation, yet the gradient is reduced. The only other important factor which is supposed to reduce the T waves, and, therefore, the size of the gradient, under the conditions of these experiments, is a change in the contact of the heart with tissues, the electrical conductivity of which differs.[12] It is unlikely that the effects of amyl nitrite can be ascribed to such a cause; and this may also be true of the changes which occur during the Valsalva experiment. Furthermore, the standing posture increases the QRS area about as often as it reduces it, yet the gradient is regularly reduced. It is reasonable to suppose that contacts between the heart and other thoracic structures should affect the magnitude of the one vector as much as they affect the other, but they are by no means equally modified. Alkalosis and acidosis[4] may be ruled out by the promptness of the changes due to posture, a point emphasized by Mayerson and Davis.[7]

In the normally beating heart, therefore, there are two conditions which are associated with a change in the magnitude of the gradient. One is the heart rate; the other is the output of blood per beat, or the stroke volume. It should be noted that we do not say that stroke volume causes the gradient; we say that, under many conditions, a larger stroke volume is associated with a larger gradient, and vice versa. Other factors may, of course, modify the effects of these two, but their nature has not been demonstrated.

*Nordenfelt's conclusion was opposite to this; but, as a matter of fact, his figures show a reduction in gradient magnitude on standing, although this is relatively small. For this reason, depression of the S-T segments did not appear.

The effect of rate may be interpreted in the light of the following unpublished experiments. The ventricle of a turtle, at room temperature, was driven at various rates, and a record made of the monophasic action current at each rate. As cycle length shortened, the duration of the monophasic curve also shortened, along a curve similar to that which shows the relation between the Q-T interval and the heart rate.[13] When the same ventricle was cooled about 10° C., its monophasic curve was nearly as short, when the cycle length was short, as was the monophasic curve of the uncooled ventricle at the *same* heart rate. But when the cycle lengths were long, the monophasic curve of the cooled muscle had nearly twice the duration of the curve from the uncooled muscle. The ventricular gradient most plausibly is a result of slower repolarization (i.e., longer monophasic curve) in some parts of the ventricles than in others. Hence, as in the turtle experiment, increasing the heart rate should cause a greater curtailment of the response in those regions which are normally slow to recover, like the cooled muscle, than in those regions which recover more promptly, like the uncooled muscle. When the durations of the excited state in the different regions become more nearly equal at higher heart rates, the electrical difference upon which the gradient depends is diminished, and, for this reason, the manifest area or magnitude of the gradient is reduced.

This interpretation satisfactorily accounts for the effect of heart rate on the gradient, although it does not prove that this is the real explanation. It throws no light whatever on the cause of those regional differences upon which the gradient depends. It is tempting to assume that the stroke volume is in some way related to the production of the normal gradient. More precisely, it may be imagined that the gradient depends upon the differential extent of shortening of subendocardial and subepicardial muscle fibers, and upon a correlated difference in energy expenditure and time required for electrical recovery. As stroke volume increases from zero, the gradient should increase, at first rapidly and then more slowly to a maximum, and should then slowly decline unless the decrease is offset by the rate effect. Most of the facts in our possession favor this interpretation, but so many uncertainties exist that an extended development of the hypothesis should not now be undertaken.

7. APPLICATION TO CLINICAL ELECTROCARDIOGRAPHY

In this and the preceding paper we have discussed factors which influence the normal direction and the magnitude of the manifest area of the QRS and of the ventricular gradient. We have given some evidence to show that the manifest area of the QRS is mainly dependent upon the direction, in relation to the frontal plane of the mean spatial QRS axis, $S\hat{A}_{QRS}$. However, it is also probably very slightly diminished during sinus tachycardia by a physiologic factor, namely, the accelerated velocity of conduction of the wave of excitation brought about

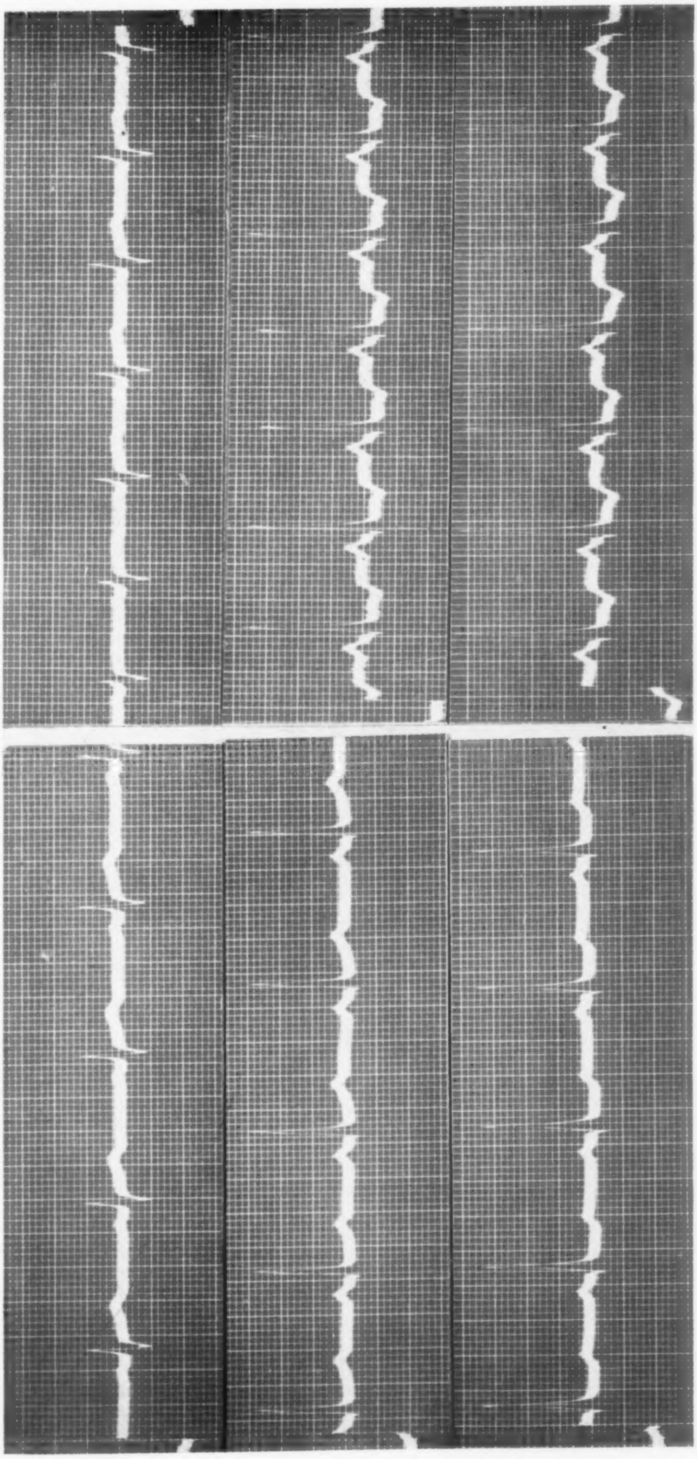

Fig. 6.—Electrocardiograms from a healthy student, aged 24, showing the effect of a change from supine to standing. This is Case 20 in Table III.

by augmented sympathetic tonus. The normal manifest area of the ventricular gradient, on the other hand, is affected not only by the direction of $S\hat{G}$, but by physiologic factors, the most important of which is heart rate. These apparently alter the magnitude of $S\hat{G}$. But the size of the gradient is also affected by another unknown factor which may be related to the stroke volume. Furthermore, the evidence thus far presented indicates that the absolute magnitudes of $S\hat{A}_{QRS}$ and $S\hat{G}$ in normal persons, under comparable conditions, differ much less than empirical observations could possibly have suggested. We believe that it is possible to make a fair estimate of the normal absolute magnitude of the vectors as they are projected in three dimensional space, and not merely on the frontal plane. This statement applies to the normal subject, for, as is well understood, abnormal changes may add to, or subtract from, that component of the vector which lies at right angles to the frontal plane without making their presence felt in the limb leads. Finally, as a rule, the three axes, namely, the longitudinal axis of rotation, H, the gradient, $S\hat{G}$, and $S\hat{A}_{QRS}$, normally lie very nearly in one plane and are separated by nearly constant angles.

If the foregoing statements are true, it then becomes possible to systematize three-lead electrocardiography so that it will not only be simpler to learn, but a more discriminating instrument for the detection of disease. Precordial leads, as hitherto, should detect those changes which produce electrical effects at right angles to the frontal plane, and what they reveal may assume new significance when correlated with the limb leads.

Our third paper will supply much additional evidence, and it will be given in a more quantitative fashion. Either in that paper, or in a subsequent one, we can consider the further question of the possible effect of thoracic shape and of structures of possibly different electrical conductivity upon the magnitude and direction of the axes. We do not deny that such effects exist, but it appears that they have relatively little effect upon the mutual relationships of the vectors.

SUMMARY AND CONCLUSIONS

Several of the factors which affect the manifest magnitudes of the mean QRS axis and of the ventricular gradient have been studied.

Both of these magnitudes are slightly smaller in women than in men, even when correction is made for the sex difference in heart rate.

Other things being equal, an increase in heart rate is associated with a decrease in the manifest magnitude of the gradient, and vice versa. The effect of increased rate is best demonstrated by a comparison of the effect of amyl nitrite and of exercise on recumbent subjects. Some subjects show a slight increase in the manifest magnitude of the gradient during the period of reflex cardiac slowing after the Valsalva experiment.

A change in posture from supine to standing invariably leads to a measurable decrease in the magnitude, G, and this change is too great to be caused by the cardiac acceleration. Often the decrease is extreme.

A comparison of the effects of the several procedures suggests that two separate factors are associated with the change in the manifest magnitude of the gradient, namely, heart rate and ventricular stroke volume.

On the average, in different subjects, the mean manifest areas of QRS and QRS-T show a direct correlation. This is interpreted in terms of a relatively fixed angle between the two axes, $S\hat{A}_{QRS}$ and $S\hat{G}$, and their projection upon the frontal plane of the body.

Two electrocardiograms are singled out for individual discussion. One, from a normal medical student, showed inversion of the T wave in Lead I when the subject was standing.

It is pointed out that the electrocardiographic approach which is being developed in these papers should not only make it possible to systematize the subject, but should also make electrocardiography a more discriminating instrument for the detection of disease.

One of the major implications of this study is that T-wave peculiarities or changes can be evaluated properly only when considered in relation to the magnitudes and directions of the mean QRS and QRS-T areas. This fact will remain true, even if it should be demonstrated that the actual magnitudes and directions of the vectors are not quite accurately given by the Einthoven triangle.

We wish to acknowledge, with thanks, the assistance given by Dr. J. L. Gouaux in making the fluoroscopic examinations, and by Dr. R. H. Bayley, who thoroughly criticized the manuscript.

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THE BENZOL-ADRENALIN TEST AS A RELIABLE METHOD OF ESTIMATING CHANGES IN THE SENSITIVITY OF THE DOG'S VENTRICLES TO FIBRILLATION. APPLICATION OF THE METHOD TO THE STUDY OF QUINIDINE SULFATE

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IN PREVIOUS papers,[1, 2, 3] we reported the effect on the "fibrillation threshold" of the dog's ventricles of several drugs (procaine, digitalis, ouabain, papaverine, epinephrine, quinidine). The "fibrillation threshold" is the strength of the weakest short direct current stimulus which will induce ventricular fibrillation when applied directly on the ventricular surface in the last 0.04 to 0.06 second of ventricular systole, the so-called "vulnerable period." In those studies, ventricular fibrillation, once induced, was immediately stopped by the alternating current countershock method, and the fibrillation threshold, which was repeatedly ascertained, was shown to be constant, provided a few simple experimental precautions were taken. Therefore, this method allowed us to quantitate the effect on the fibrillation threshold of several physiologic,[4] pharmacologic,[1, 2, 3] and pathologic factors.[5] This procedure is rather difficult and tedious in execution, and we therefore tested a simpler method of estimating the sensitivity of the mammalian ventricles to fibrillation.

It is well known[6] that several drug combinations, such as chloroform-adrenalin, benzol-adrenalin, and cyclopropane-adrenalin, may induce ventricular fibrillation. Shen and Simon[7] and Burstein and Marangoni[8] made use of such drug combinations to study the action of procaine. They showed that procaine decreases the sensitivity of the mammalian ventricles to both chloroform-adrenalin[7] and cyclopropane-adrenalin[8] and prevents ventricular fibrillation. But, since ventricular fibrillation, once induced, leads to the death of the animal, their studies and similar ones consisted in comparing the reaction to chloroform-adrenalin, benzol-adrenalin, or cyclopropane-adrenalin of a control group of dogs with that of another group which received the protective drug. This statistical method of estimating the ability of a drug to prevent ventricular fibrillation is not entirely convincing, however, because, when a group of dogs are tested with chloroform-adrenalin, cyclopropane-adrenalin, and, to a lesser extent, benzol-adrenalin, some develop ventricular fibrillation, some show impressive runs of ventricular tachycardia, and others

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display only a few scattered ventricular extrasystoles.[6, 9] On the other hand, any given dog, under constant experimental conditions, reacts constantly to the benzol-adrenalin combination. For this reason, repeated tests on the same dog before and after the administration of a drug are much more reliable as regards the efficacy of the drug under study.

In order to be conclusive, it is necessary to prove (1) that a dog's heart which develops ventricular fibrillation from benzol-adrenalin can be revived with an alternating current countershock; and (2) that such a heart, when repeatedly revived, will react repeatedly in the same way, and for a reasonable length of time, to benzol-adrenalin. These two requirements can be satisfactorily met, as is shown by the experiments reported in this paper.

METHOD

Dogs which weighed an average of 10 kilograms were anesthetized by the intravenous administration of 300 to 350 mg. per kilogram of sodium barbital. Under artificial respiration, the chest was opened through a midsternal incision and the heart suspended in a pericardial cradle. The mean arterial blood pressure was recorded on a kymograph from the femoral artery. An electrocardiographic tracing, generally Lead III, was recorded from subcutaneous electrodes. A standardized benzol-adrenalin test was performed as follows: Benzol was administered by intratracheal inhalation through an anesthesia bottle until the mean blood pressure fell 20 to 40 mm. Hg. Then, simultaneously, the administration of benzol was stopped and 0.02 mg. per kilogram (1:10,000 solution) of adrenalin was administered via the jugular vein. As soon as ventricular fibrillation was induced, two electrodes padded with cotton soaked in Locke's solution were applied around the ventricles, and short runs of a 60 cycle per second alternating current, 2 to 3 amperes in strength, were sent through the heart until the fibrillation stopped. A recovery period of at least fifteen minutes was allowed after fibrillation was stopped.

RESULTS

The results obtained in testing quinidine sulfate are illustrated by Fig. 1 and Fig. 2, which are pictures of the series of benzol-adrenalin tests performed in two typical experiments.

In the experiment of Fig. 1, the dog's mean blood pressure was 120 mm. Hg at 12:05 P.M. Benzol was then administered by tracheal inhalation. When the blood pressure had decreased to 70 mm. Hg, benzol was withdrawn and 0.02 mg. per kilogram of adrenalin was injected into the jugular vein. The blood pressure rose to 150 mm. Hg, and then ventricular fibrillation developed suddenly. The heart was immediately revived by the alternating current countershock method. At 12:45 P.M. a similar administration of benzol and adrenalin (0.02 mg. per kilogram) initiated ventricular fibrillation which was promptly stopped again with our reviving method. At 1:00 P.M. 15 mg. of quinidine sulfate (one per cent solution) per kilogram were administered via the femoral vein over a period of ten minutes. The blood pressure dropped from 110 mm. Hg to 50 mm. Hg. At 1:15 P.M. benzol-adrenalin (0.02 mg. per kilogram) did not produce fibrillation, although the blood pressure rose from

45 mm. Hg to 85 mm. Hg, but not as suddenly as in the control tests. Four more times the test was repeated. Arrhythmias, especially runs of ventricular tachycardia, developed, but ventricular fibrillation never occurred, despite the fact that in the last test, for example, the blood pressure rose from 65 mm. Hg to 115 mm. Hg, not very suddenly, however. At 3:05 P.M., i.e., almost two hours after the end of the quinidine

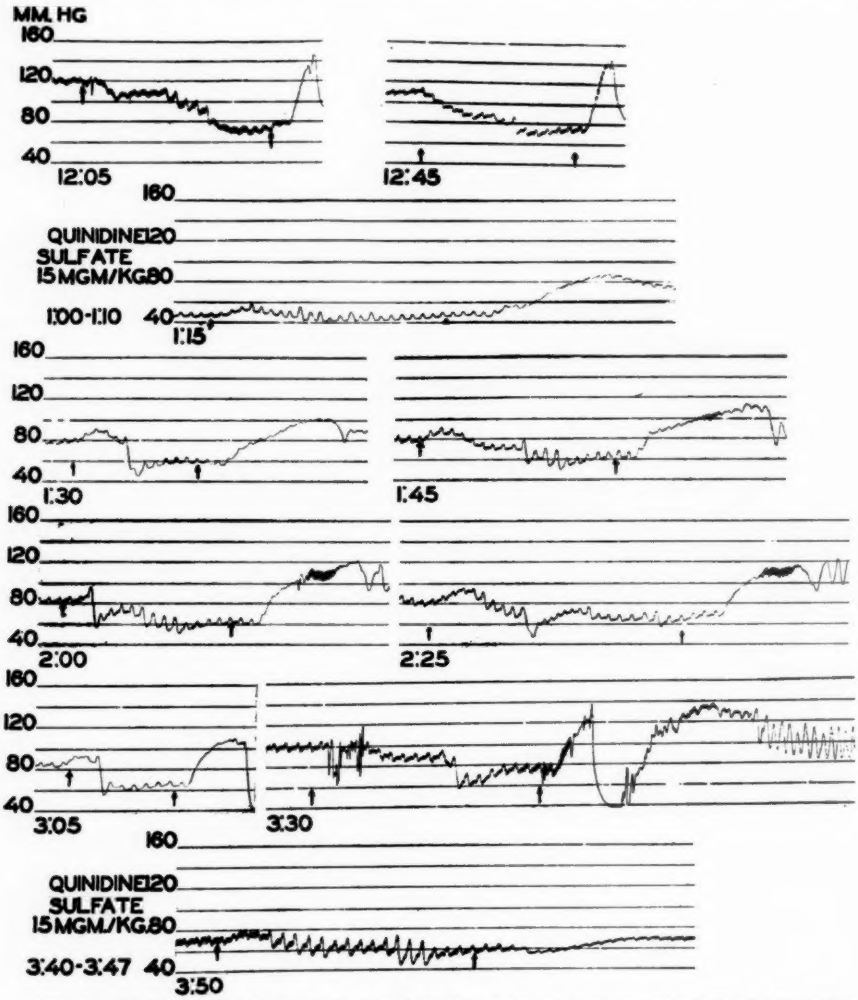

Fig. 1.—Tracing of the mean femoral blood pressure during each benzol-adrenalin test performed in a typical experiment during which rather large doses of quinidine sulfate were administered. Numerals on the left refer to mm. Hg and are the scale for the femoral blood pressure. Numerals below the tracing of each test refer to the time at which the test was performed.

administration, benzol-adrenalin (0.02 mg. per kilogram) induced ventricular fibrillation, although the blood pressure did not rise more (from 65 mm. Hg to 110 mm. Hg) or more suddenly than in the preceding tests in which fibrillation did not occur. At 3:30 P.M., benzol-adrenalin (0.02

mg. per kilogram) produced fibrillation again; the blood pressure rose from 80 mm. Hg to 140 mm. Hg. Fig. 1 shows the tracing of the mean arterial blood pressure before, during, and after revival from fibrillation by the alternating current countershock during this test. Between 3:40 and 3:47 P.M., another dose of 15 mg. per kilogram of quinidine sulfate was administered via the femoral vein, and, later on, benzol-adrenalin (0.02 mg. per kilogram) failed to induce ventricular fibrillation.

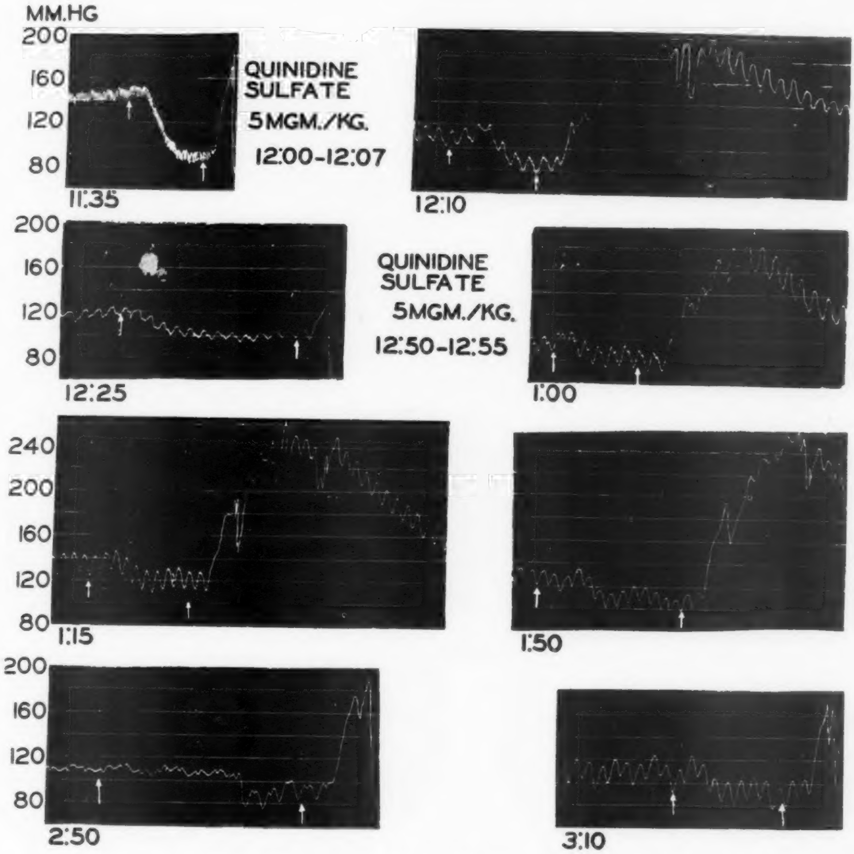

Fig. 2.—Tracing of the mean femoral blood pressure during each benzol-adrenalin test performed in a typical experiment during which smaller doses of quinidine sulfate were administered. Numerals on the left refer to mm. Hg and are the scale for the femoral blood pressure. Numerals below the tracing of each test refer to the time at which the test was performed.

This experiment evidently shows that quinidine sulfate prevented the fibrillation induced by benzol-adrenalin; yet, when the effect of quinidine was over, the heart still responded to benzol-adrenalin by developing fibrillation, which proves that the dog had remained under constant experimental conditions except for the administration of quinidine. A second administration of quinidine again prevented the benzol-adrenalin fibrillation.

The experiment of Fig. 2 is interesting in that small doses of quinidine sulfate, comparable to those used in the experiments reported by Wégria and Nickerson,[3] were used.* At 11:35 A.M., after benzol inhalation, 0.02 mg. per kilogram of adrenalin increased the blood pressure from 90 mm. Hg to 180 mm. Hg and induced ventricular fibrillation, which was stopped by the alternating current countershock. From 12:00 to 12:07 P.M., 5 mg. per kilogram (1 per cent solution) of quinidine sulfate were administered via the femoral vein. The mean femoral blood pressure dropped from 120 to 100 mm. Hg. At 12:10 P.M., it was about 110 mm. Hg, and benzol-adrenalin (0.02 mg. per kilogram) did not produce ventricular fibrillation, although the blood pressure rose from 80 to 200 mm. Hg. At 12:25 P.M., benzol-adrenalin (0.02 mg. per kilogram) was administered; the blood pressure rose from 100 to 130 mm. Hg, and then fibrillation developed suddenly. After revival and recovery, an additional 5 mg. per kilogram of quinidine sulfate were administered. The arterial blood pressure temporarily dropped from 100 to 85 mm. Hg but soon stabilized around 95 mm. Hg and, at 1:00 P.M., benzol-adrenalin (0.02 mg. per kilogram) did not produce fibrillation, although the blood pressure rose from 70 to 185 mm. Hg. In two more similar benzol-adrenalin tests, at 1:15 and 1:50 P.M., fibrillation did not develop, and yet, in both tests, the blood pressure rose as suddenly and as high as or higher than in the control tests. At 2:50 and 3:10 P.M., respectively, two similar benzol-adrenalin tests induced fibrillation, but the blood pressure did not rise higher or more suddenly in these last two tests than in the preceding ones in which fibrillation did not develop.

This series of experiments shows that quinidine sulfate, in doses of about 15 mg. per kilogram, protects the dog's ventricles against the benzol-adrenalin fibrillation. With such doses of quinidine, the mean arterial blood pressure is significantly reduced for some time. In benzol-adrenalin experiments after the administration of such doses of quinidine, ventricular fibrillation does not develop, whether or not the blood pressure rises as much and as suddenly as in control tests. That protection lasts for some time.

Smaller doses of quinidine sulfate (5 mg. per kilogram) decrease the mean arterial blood pressure very slightly and only temporarily. During a benzol-adrenalin test after such doses of quinidine sulfate, the increase of blood pressure is the same or sometimes even greater than in a test before the administration of quinidine; nevertheless, such doses of quinidine protect the heart against benzol-adrenalin.

*In these experiments, the sinus node was clamped; the heart was driven at a constant and rather high rate by applying induction shocks to the right ventricle, and the fibrillating direct current stimulus was applied on the left ventricle. With such a preparation, we were never able to successfully use doses of quinidine sulfate greater than 2 mg. per kilogram, because larger doses depressed the myocardium and blood pressure too much and caused the heart to go progressively into failure. Apparently, hearts driven at a high rate by means of an artificial pacemaker cannot tolerate as much quinidine as do normally beating hearts.

SUMMARY

1. A new method of ascertaining repeatedly, in the same animal, the sensitivity of the dog's ventricles to fibrillation is presented.

2. This method is easier to perform than the "fibrillation threshold test," and yet it is critical. However, it does not quantitate the sensitivity to fibrillation. The procedure consists in comparing the reaction of the same dog to the combination of benzol-adrenalin befo. nd after the intervention of some factor under study, such as a drug. This is done by ascertaining whether or not benzol-adrenalin, which induces fibrillation before the administration of the drug to be studied, still does so after the administration of the drug.

Whether or not the sensitivity of the heart to the benzol-adrenalin fibrillation could be quantitated by ascertaining the amount of adrenalin required to produce fibrillation remains to be studied.

3. Quinidine sulfate protects the dog's ventricles against benzol-adrenalin and prevents the benzol-adrenalin fibrillation, which confirms the results we obtained by the fibrillation threshold method.

4. The protection exists whether or not the dose of quinidine sulfate administered diminishes the increase of blood pressure which normally occurs during a control benzol-adrenalin test.

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THE INCIDENCE OF RHEUMATIC STIGMAS IN HEARTS WHICH ARE USUALLY CONSIDERED NONRHEUMATIC

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IN A previous study,[1] an attempt to find normal hearts which were free from rheumatic stigmas when examined microscopically according to the standard method of Gross, Antopol, and Sacks[2] was unsuccessful. Correlated with this fact is the observation at the autopsy table that one or more cardiac valves nearly always show some small degree of thickening in patients who had no clinical manifestations of endocarditis. The mitral valve is the one involved by far the most frequently (Fig. 1). Thickening is best observed along the line of closure. Often there is slight thickening, and, in some instances, there are adhesions among the chordae tendineae. The aortic valve may show slight adhesions along the commissures, and one or more leaflets of the tricuspid valve are often thickened and somewhat opaque in appearance. These considerations have induced us to investigate further the incidence of rheumatic stigmas in hearts which are usually considered to be free from rheumatic infection.

METHODS AND MATERIALS

A preliminary study was made of thirteen hearts which showed no valvular lesions save the minimal changes referred to above. Standard blocks were taken: one through each of the four valves, one from the posterior papillary muscle of the left ventricle, and the sixth block from the wall of the left auricle. The blocks were embedded in paraffin. Microscopic sections were stained with hematoxylin and eosin and with MacCallum's elastic tissue stain, and counterstained by van Gieson's method. Rheumatic stigmas were found quite abundantly in nine of these hearts, and somewhat sparsely in four of them. It was therefore decided to proceed with a larger number of cases. The preliminary study indicated that the block from the posterior papillary muscle was the most useful one for our purposes. Since it was necessary to depend for procurement of material largely on the cooperation of our residents in pathology, it was decided to ask routinely for blocks of the posterior papillary muscle (the anterior was used if it was larger than the posterior) and a block through the base of the left ventricle, including a portion of the posterior mitral leaflet and a small portion of the left auricle. It seemed to us more important to examine a large number of hearts in this way than a lesser number by the more complete method. We believe our data justify this decision. About 25 per cent of the material was obtained from autopsies performed by one of us (E. M. H.). Multiple blocks of the heart were obtained in many of these cases.

In all, 124 hearts were studied. Some of these, purposely included, contained recent or healed rheumatic valvular lesions or were the seat of bacterial endocarditis. This group of 12 hearts was used as a control series.

The larger group, consisting of 112 hearts, was free of gross, deforming valvular lesions, and in none of these cases had there been clinical evidence of rheumatic infection or chronic valvular disease.

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RHEUMATIC STIGMAS

The various stigmas were those commonly considered to be rheumatic. These were grouped under three headings, viz., vascular, perivascular, and interstitial. Essentially the same stigmas were used by Hall and Ichioka[1] in a previous investigation of calcific aortic stenosis. *Vascular lesions* included arteritis rheumatica, fibrinoid necrosis, and elastic tissue alterations. Under the heading of *perivascular lesions*, Aschoff nodules, fibrinoid swelling, and cellular infiltration were considered. The only *interstitial lesion* taken into account was cellular infiltration. Cellular myocardial scars caused by vascular changes of rheumatic origin were encountered in a number of instances. These are so difficult to separate from the scarring caused by arteriosclerosis of the coronaries that it was thought best not to include myocardial scarring. Edema is important in acute rheumatic lesions, but it is most likely to arise from other causes in the chronic forms.

Fig. 1.—Autopsy 22190. Ethiopian female, aged 30 years. Heart weight 310 Gm. Photograph of the heart showing a slightly nodular fibrous thickening of the leaflets of the mitral valve along their closing edges. Several of the chordae tendineae appear to be slightly thickened. The papillary muscles are hypertrophied.

Vascular and Perivascular Lesions.—Rheumatic lesions of the coronary arteries have been thoroughly studied by Karsner and Bayless.[3] Von Glahn and Pappenheimer,[4] in 1926, described in detail the peripheral vascular changes in acute rheumatic infections. These authors speak of swollen endothelium and swelling of the vessel wall, with reduction in the size of the lumen. In the acute phase, swelling is the result of infiltration of the walls with fibrin. Klinge[5] refers to this as "fibrinoid Verquellung," and the accompanying necrosis he calls "fibrinoid necrosis." In acute rheumatic fever the infiltrating fibrin can be stained dark blue with Weigert's fibrin stain, yellow with van Gieson's stain,[4] and pink with eosin (Fig. 2). In the chronic lesions of rheumatic heart disease, a fine, hyaline, fibrillary substance is found about the coronary arterioles in many instances. The wall of the arteriole may contain hyaline, finely granular patches (fibrinoid necrosis), or the wall may be thickened and completely hyalinized (Figs. 3 and 4).

Although the hyaline, fibrillary material about the vessel optically resembles fibrin, it no longer takes the fibrin stain. As von Glahn and Pappenheimer[4] state, the fibrinous exudate is gradually changed into a permanent tissue (Fig. 5). This material now stains faintly red with van Gieson's stain and blue with Mallory's connective tissue stain. These perivascular scars are apparently healed phases of the fibrinoid reaction. Likewise, the hyalinized wall of the arteriole is also fibrous (Figs. 4 and 5).

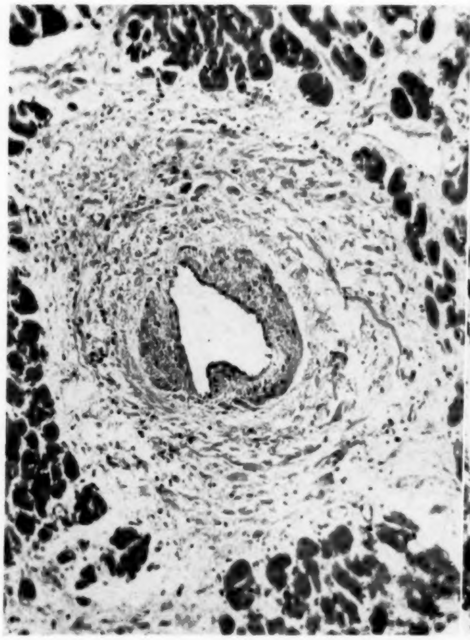

Fig. 2.

Fig. 3.

Fig. 2.—Autopsy S-4718. Caucasian male, 22 years of age. Heart weight 940 Gm. *Control case.* (Rheumatic heart disease and bacterial endocarditis.) This microphotograph of the heart illustrates fibrinoid necrosis and swelling of a coronary arteriole, also perivascular fibrinoid swelling as seen in a more acute phase. (H and E 100×.)

Fig. 3.—Autopsy 22305. Caucasian female, 61 years old. Heart weight 300 Gm. The microphotograph shows slight swelling and patchy fibrinoid necrosis of the wall, also some hypertrophy of the endothelium. (H and E 250×.)

Rheumatic arteritis has been used by us in a broad sense to include endothelial hyperplasia and hypertrophy, disarrangement of muscular elements (metallaxis), which is a characteristic and common feature in rheumatic infections, and infiltration of inflammatory cells within the vessel wall. The latter consist chiefly of large mononuclear cells (cardiac histiocytes), with a few lymphocytes, and occasional eosinophils. Since varying degrees of fibrinoid necrosis are usually present, there is a reduction in the number of smooth muscle nuclei, and those that remain often appear pyknotic (Figs. 6 and 7). Rheumatic arteritis is much more common in the acute rheumatic lesions than in the healed ones.

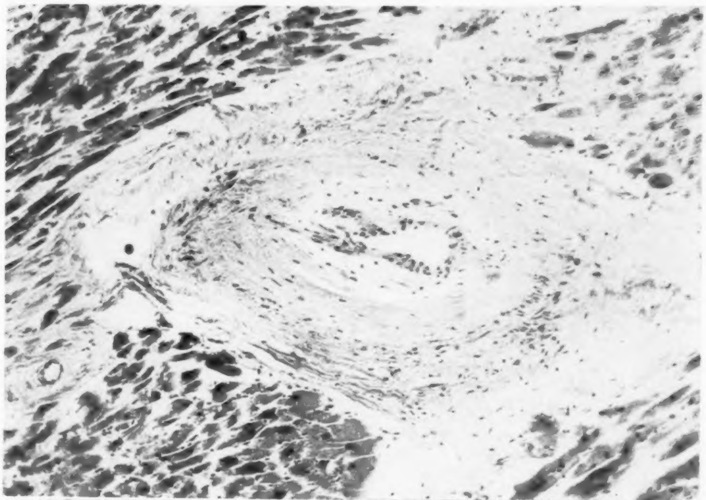

Fig. 4.

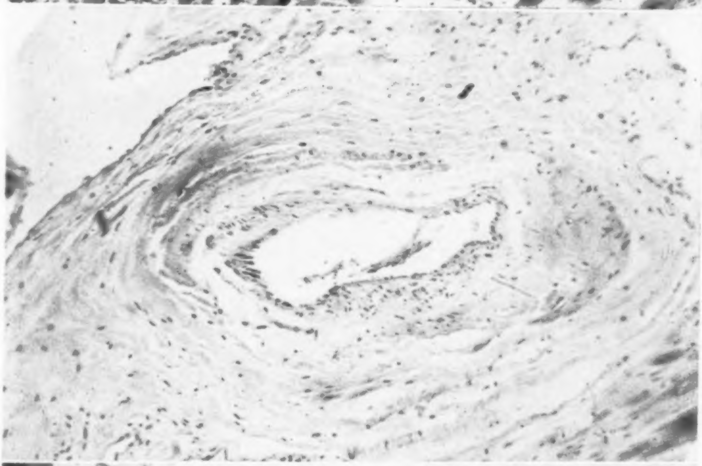

Fig. 5

Fig. 6.

Fig. 4.—Autopsy S-4409. Caucasian male, 63 years old. Heart weight 525 Gm. Microphotograph illustrating swelling or thickening of the vessel wall, with hyaline fibrous changes, probably the result of fibrinoid necrosis. The lumen is considerably narrowed. (H and E 130×.)

Fig. 5.—Autopsy 25731. Caucasian female, 86 years old. Heart weight 410 Gm. This microphotograph of a coronary vessel shows much the same thing as Fig. 4, with the addition of a perivascular hyaline fibrillary mass which optically resembles fibrinoid swelling. This is, however, permanent fibrous tissue. (H and E 100×.)

Fig. 6.—Autopsy S-4388. Caucasian male, aged 29 years. Heart weight 225 Gm. (Acute glomerulonephritis.) Microphotograph of a coronary artery showing pale areas of patchy necrosis alternating with areas of increased cellularity (histiocytes). This is an example of arteritis. (H and E 250×.)

Fig. 7.

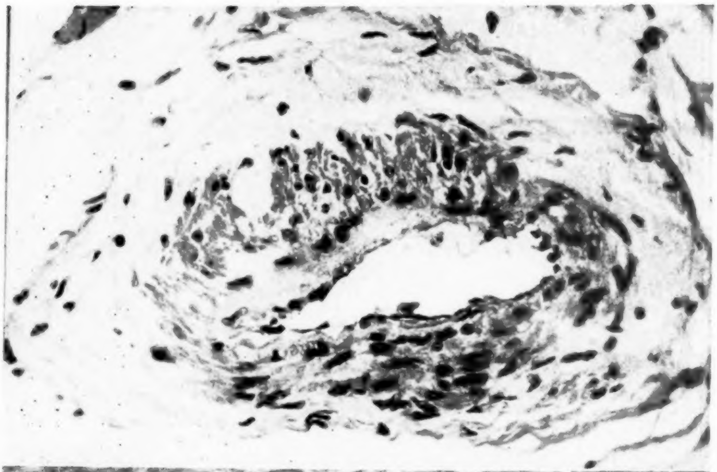

Fig. 8.

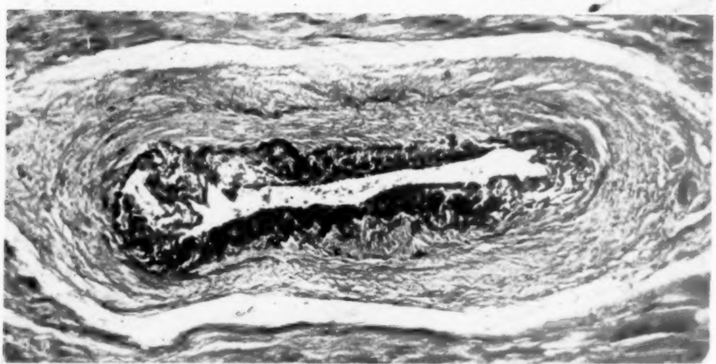

Fig. 9.

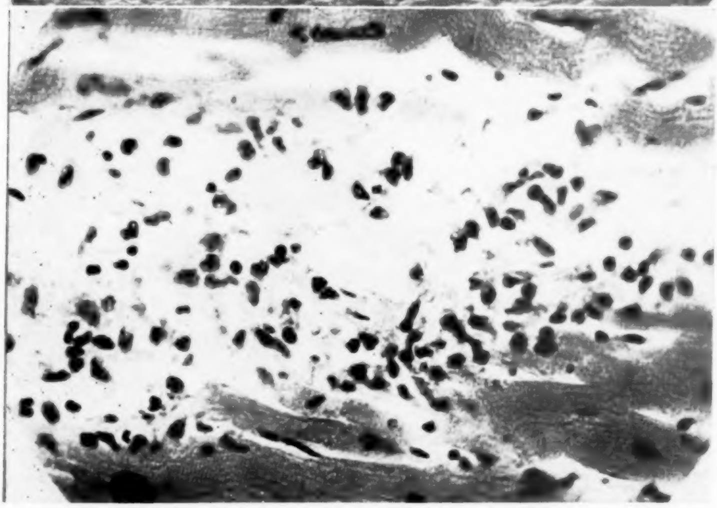

Fig. 7.—Autopsy S-4388. Same patient as in Fig. 6. Microphotograph illustrates same features as in Fig. 6, and, in addition, shows subendothelial edema, hypertrophy of endothelium, metallaxis, and perivascular fibrinoid swelling. (H and E 250×.)

Fig. 8.—Autopsy 25138. Caucasian male, aged 53 years. Heart weight 350 Gm. Microphotograph of a coronary artery showing alterations in the elastic tissue. The elastica appears greatly thickened, apparently because of splitting, fraying, and swelling of fibers. (MacCallum elastica stain and van Gieson stain.) (100×.)

Fig. 9.—Autopsy 25138. Same patient as in Fig. 8. Microphotograph showing a large collection of cardiac histiocytes or Aschoff cells. Aschoff body. (H and E 450×.)

As would be expected, therefore, only a few specimens revealed a marked degree of arteritis, but many presented minor changes of this character.

Elastic Tissue Alterations.—According to von Glahn and Pappenheimer,[4] the elastic tissue changes are well marked in acute rheumatic infections. These authors describe swelling and beading of the elastica interna and alteration in the staining reaction. When exudation of fibrin is abundant, the lamellae may be difficult to distinguish and may disappear. Karsner and Bayless[3] found elastica alterations in 90 per cent of their cases in the first two decades, and in all subsequent cases. They describe swelling, splitting, and fragmentation of elastic lamellae. Although many infections injure the elastica, these authors found that rheumatic fever produces early and serious damage to the elastica of the coronary arteries. Superficially, the elastica changes in our specimens appeared to be the result of hyperplasia. On closer study it was found that the process consists of swelling, splitting, fraying, and smudging (Fig. 8). Some degree of elastic tissue alteration was present in practically all of our hearts and was marked in nearly half of them.

Aschoff Bodies.—Most investigators accept the Aschoff body as a specific lesion of acute rheumatic heart disease. Aschoff bodies in chronic rheumatic lesions are not as characteristic as in the acute lesions.[1, 6] In his monograph on rheumatism, Klinge[5] describes and illustrates with a colored plate what he believes are the steps in the life cycle of the Aschoff nodule. After the typical granuloma stage, as seen in acute cardiac lesions, involutionary changes set in which cause the giant cells, fibrin, and hyaline matrix to disappear gradually; they are replaced by scar tissue which is more or less cellular. We agree with Klinge,[5] Gross and Ehrlich,[6] and others that the Aschoff body undergoes a series of changes as the rheumatic infection goes into a more chronic phase. Some Aschoff nodules lose their cellularity completely, and new ones appear with recurrent attacks of the disease. Masses of hyaline collagenous material are usually not present in the centers of Aschoff nodules during the chronic phase (Figs. 9 and 10).

Clawson[7] has recently described the chief cell of the Aschoff body. This is a large, somewhat elongated mononuclear cell with a long, bar-like nucleus which gives off fine processes that extend through the cytoplasm toward the periphery. In cross section the nucleus is irregular in outline and appears to be suspended near the center of the cell by radiating lines of fibrillar material which pass outward to the cell membrane. According to Clawson,[7] it is generally agreed that this cell develops from cardiac interstitial tissue and that it is restricted in its location to the myocardium and cardiac valves. He agrees with Downey that the cell should be called a cardiac histiocyte. Klinge[5] uses the term "mesenchymal cells." These special histiocytes apparently increase in the myocardium under the stimulus of various irritants. Acute infections

caused by the pyogenic cocci call out polymorphonuclear neutrophils, as in other organs. Lymphocytes and plasma cells also appear in the myocardium in various chronic infections. Acute and subacute infections of the rheumatic type call out these particular histiocytes in considerable numbers. Occasionally the reaction is more exudative in type, causing an abundant fibrinoid reaction and a minimal proliferative response. Even so, nests of cardiac histiocytes (Aschoff bodies) may be found. It would seem, therefore, that cardiac histiocytes are not specific for rheumatic infections, but are specific as to the cardiac reaction to certain irritants. The response to the rheumatic virus is usually very active. They are likewise found abundantly in bacterial endocarditis, acute glomerulonephritis, and other streptococcal infections. The specimens in our series in which the other rheumatic stigmas were well represented were the ones in which Aschoff bodies were most frequently found.

Perivascular and interstitial nestlike collections of cardiac histiocytes we have called Aschoff nodules. If the cells are more loosely arranged and not so abundant we have referred to them as sub-Aschoff bodies or Aschoff-like nodules (Fig. 11).

Histiocytic Cellular Infiltration.—The perivascular and interstitial histiocytic response refers to an increase in the number of cardiac histiocytes in these areas. If the number of histiocytes was greatly increased, Aschoff nodules were almost invariably present. In a number of specimens in which histiocytes were abundant both about the vessels and in the interstitial spaces, multiple Aschoff nodules were found. In general, the histiocytic infiltration was the most variable among the stigmas considered.

Relation to Hyperergy.—A number of authors have expressed the view that the tissue changes in rheumatic fever are the result of hypersensitivity to some antigen, usually streptococci. Swift, Derrick, and Hitchcock,[8] in 1928, expressed their views very clearly on this subject. Klinge[5] has been the outstanding exponent in Europe of the view that rheumatic fever is related to hyperergy, and Rössle[9] and Chiari[10] are in agreement with him. Many names might be added to the list; in fact, it may be stated that the idea of hypersensitivity in relation to rheumatic infections is quite widely accepted. Although the etiology is not known, various types of streptococci have been so frequently associated with acute rheumatic manifestations that many investigators believe that they are etiologically important, if not the actual cause of the disease.

By repeated parenteral injections of horse serum in rabbits, Klinge[11] was able to produce a hyperergic arthritis, accompanied by Aschoff-like granulomatous lesions about the small coronary arteries. Vaubel,[12] employing the same experimental procedure, likewise obtained hyperergic carditis. Small quantities of horse serum, injected subcutaneously at intervals of several weeks, provoked a mild response, and larger amounts, by the intravenous route, resulted in a severe hyperergic

Fig. 10.

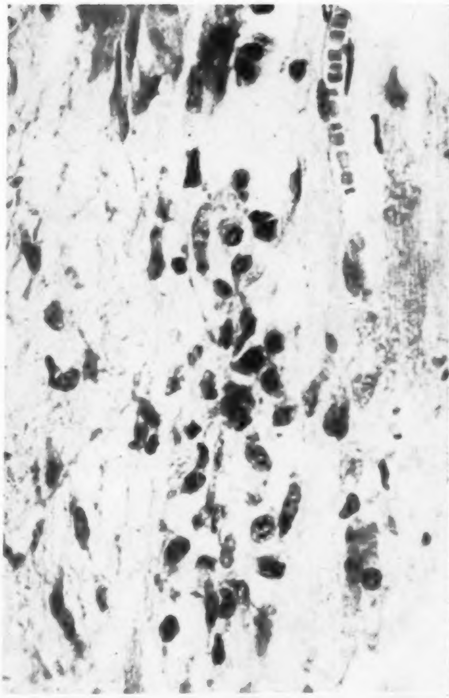

Fig. 11.

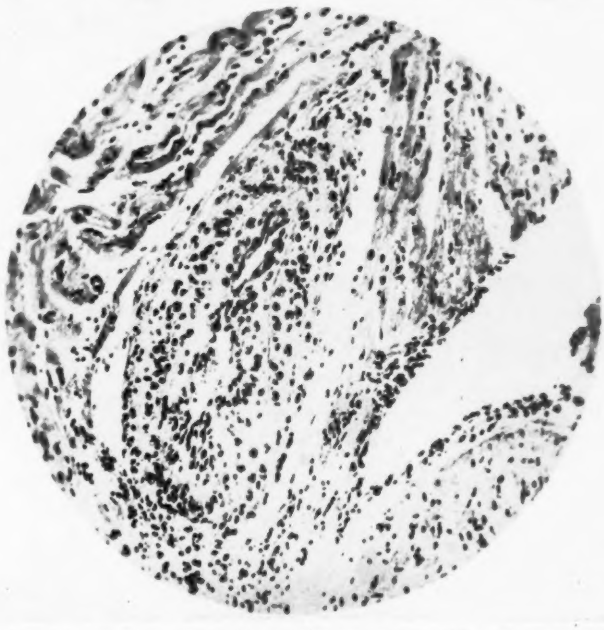

Fig. 12.

Fig. 10.—Autopsy 26208. Caucasian male, 60 years old. Heart weight 650 Gm. Microphotograph showing collection of cardiac histiocytes to form an Aschoff body. (H and E 400×.)

Fig. 11.—Autopsy 22305. Caucasian female, 61 years of age. Heart weight 300 Gm. Microphotograph illustrating a loose collection of perivascular cells, mainly histiocytes. Such collections the authors have called Aschoff-like or sub-Aschoff bodies. (H and E 200×.)

Fig. 12.—Experimental lesion in a coronary artery of a rabbit produced by multiple injections of horse serum intravenously in large doses (2-20 c.c.) over a period of 6 to 7 weeks. The microphotograph shows endothelial hyperplasia, edema of the subendothelial layer, and marked increase in histiocytes throughout the muscularis. There is some perivascular increase in mononuclear cells, also infiltration of the endocardium with similar cells. (H and E 100×.)

TABLE I

CONTROL CASES (KNOWN RHEUMATIC OR BACTERIAL ENDOCARDITIS)

			CARDIAC VALVES THICKENING					VASCULAR			PERIVASCULAR					
NO.	AGE AND SEX	HT. WT.	HISTORY RHEUM. FEVER	FUSION COMMISSURES	AORTIC	MITRAL	TRICUSP.	ARTERITIS	FIBRINOID NECROSIS	ELASTIC TISSUE HYPERPLASIA	ASCHOFF BODY	FIBRINOID SWELLING	CELLULAR INFILTRATION	INC. MESEN. CELLS	PERICARDIUM	PRINCIPAL LESIONS
1	M 8	345	+	–	–	–	–	++	++	++	+	+++	+++	+++	+	Rheu. pericard. (subac.) Myocarditis (acute)
2	F 9	300	+	–	–	+	–	++	++	+++	+	+++	+++	++	+	Rheu. pancarditis. Subac. pericarditis.
3	Mex. M 12	250	+	–	–	ch. veg.	–	++	++	+++	+	+++	++	+++	+	Ac. bact. endocard. Osteomyelitis. Abscesses myocardium.
4	M 22	940	10 yr. +	–	rolled +	veg. +	–	++	+++	+++	+	++	+++	+++		Subac. bact. endocard.
5	M 37	440	N.R.	–	–	veg. + rolled	–	+++	+++	+++	+	+++	+++	+++		Ac. rheu. heart disease.
6	M 37	500	+	–	+	++	+	++	++	+++	–	+++	+	+		Rheu. heart disease. Mitral stenosis.
7	M 39	960	N.R.	–	veg. ++ rolled	veg. ++ nod.	–	+	+	++	±	++	++	++		Chr. rheum. endocard. Subac. bact. endo. Syph. aortitis w. insuff.
8	M 54	745	+	+	++	+	–	+	+++	++	–	+++	+	+		Chr. rheu. endocard.
9	F 54	550	Chorea	–	veg. +	+	–	+++	++	++	+	+++	+++	++	+	Ac. bact. endocard. Ac. fibrinous pericard. Rupture of heart.
10	Col. F 58	480	+	+	–	++	–	++	+++	+++	+	+++	+	++		Rheu. heart dis. Mitral stenosis.
11	M 65	660	N.R.	–	–	veg.	–	++	+++	+++	+	+++	++	+++		Bact. endocard. (Str. viridans)
12	M 75	500	+	–	veg. +	–	–	++	++	++	+	+++	+++	++		Adenoca. sig. colon. Chr. rheum. endocard. Bact. endocard.

carditis with profound involvement of the coronary arteries. Hemken,[13] working in our laboratory, produced similar results in rabbits by 9 to 10 intravenous injections of horse serum over a period of 6 to 7 weeks. Mild lesions were produced by small doses of 0.5 c.c. to 2.0 c.c. Profound changes were obtained with larger doses, ranging from 2 to 10 c.c. These changes closely parallel those of rheumatic arteritis in man; in fact, all of the stigmas described above are duplicated, including even granulomatous nests of histiocytes. An excellent example of experimental hyperergic arteritis is presented in Fig. 12.

RESULTS

Controls.—As stated previously, 12 cases of proved rheumatic and/or bacterial endocarditis were used as controls (Table I). The ages ranged from 8 to 75 years. There were 9 males and 3 females. A history of rheumatic fever was obtained in 8 cases, and of chorea in 1 case; there was no record in 3 cases. The smallest heart (250 Gm.) was from a Mexican boy, 12 years of age. All of the hearts were enlarged; the two largest weighed over 900 Gm. Mycotic vegetations were present on the mitral valve leaflets in only 6 cases and on both mitral and aortic in 1 case. In four of the remaining cases there were only healed rheumatic lesions. No valvular lesions were evident in a boy of 8 years, although subacute rheumatic pericarditis and myocarditis were present. In two cases of subacute bacterial endocarditis no previous rheumatic lesions were demonstrated.

The various stigmas of rheumatic infection were well represented in all but one case, as shown in Table I. In this case (No. 7), a man of 39 years, there was a combination of chronic rheumatic valvular disease and mycotic vegetations affecting both mitral and aortic valves, together with syphilitic aortitis and aortic insufficiency. Aschoff nodules were present in 9 cases (75 per cent), a sub-Aschoff nodule in one, and in two cases no specific granulomas were found.

Main Group of 112 So-Called Nonrheumatic Hearts.—A history of rheumatic fever was recorded in only 3 cases, a negative history was found in 16, and no record was obtained in 88. Frequent sore throats were recorded in 2 instances, and there was a history of scarlet fever in 5.

Incidence of Minimal Valve Thickening.—The minimal lesions, in the form of thickening of valve leaflets, fusion of commissures of the aortic valve, and thickening of chordae tendineae are presented in Table II.

TABLE II

SUMMARY OF GROSS CHANGES IN CARDIAC VALVES

	FUSION OF COMMISSURES	THICKENING OF LEAFLETS			THICKENING OF CHORDAE	
		AORTIC	MITRAL	TRICUSPID	MITRAL	TRICUSPID
No. cases (+)	14	10	65	22	42	9
No. cases (++)	0	3	9	0		
Total	14 (12.5%)	13 (11.6%)	74 (66.0%)	22 (19.6%)	42 (37.5%)	9 (8.0%)

TABLE III

SUMMARY OF RHEUMATIC STIGMAS IN 112 HEARTS

	VASCULAR						PERIVASCULAR						INTERSTITIAL	
	ARTERITIS RHEUM.		FIBRINOID NECROSIS		ELASTIC T. ALTERATION		ASCHOFF BODIES		FIBRINOID SWELLING		CELLULAR INFILTRATION (HISTIOCYTIC)		CELLULAR INFILTRATION (HISTIOCYTIC)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Slight (+)	31	27.7	12	10.7	7	6.16	*34	30.3	10	9.0	46	41.0	47	42.0
Mod. (++)	69	61.6	24	21.4	52	46.4	33	29.5	65	58.0	51	45.5	52	46.4
Marked (+++)	9	8.03	76	67.8	53	47.3	0		37	33.0	13	11.6	9	8.03
Absent (-)	3	2.70	0		0		45	40.18	0		2	1.87	4	3.5
Total	112		112		112		112		112		112		112	

*Sub-Aschoff bodies.

In 14 instances (12.5 per cent) the aortic commissures were fused to a slight degree (+). The aortic cusps were slightly (+) thickened in 13 cases (11.6 per cent). The mitral leaflets were the seat of minor thickening in 74 cases (66.0 per cent). The chordae tendineae of the mitral valve were thickened in some degree in 42 instances (38.4 per cent). The tricuspid leaflets were slightly (+) thickened in 22 cases (19.6 per cent). All of these percentages are probably low because most of the hearts were described by residents in pathology who in many instances failed to record minimal changes in the valves. In spite of this fact the mitral valve was thickened in 66 per cent of the specimens.

Incidence of Microscopic Rheumatic Stigmas.—These are presented in Table III. The arteritis was mainly slight to moderate. Fibrinoid necrosis, fibrinoid perivascular scarring, and elastic tissue alterations were principally in the moderate (++) and marked (+++) columns. Aschoff bodies were found in 33 instances, or 29.5 per cent, of the cases, and sub-Aschoff nodules in practically the same number, i.e., 34 times, or 30.3 per cent. In forty-five cases there were no cell nests that could be classified as Aschoff bodies.

Increase in perivascular and interstitial histiocytes was chiefly slight to moderate. There was a marked increase in roughly 10 per cent of the specimens.

TABLE IV

INCIDENCE OF MINIMAL, HEALED RHEUMATIC INFECTION IN 112 HEARTS, SHOWING ALSO DISTRIBUTION ACCORDING TO DECADES

		RHEUMATIC INFECTION		
NO. OF CASES	AGES (DECADES)	POSITIVE	PROBABLE	DOUBTFUL
3	0-10	2	1	0
3	11-20	1	2	0
6	21-30	2	3	1
9	31-40	5	3	1
18	41-50	13	4	1
22	51-60	14	7	1
29	61-70	16	11	2
17	71-80	10	5	2
5	81-90	5	0	0
Total 112		68 (60.7%)	36 (32.1%)	8 (7.2%)

The distribution of cases by ages (decades) and the number of those classified as positive, probable, or doubtful as regards rheumatic infection are recorded in Table IV. Comparatively few cases (21) fell in the first four decades. This is because the majority of patients in the Los Angeles County Hospital are in the older groups. Of five cases in the ninth decade, all were considered positive for rheumatic infection, i.e., healed lesions were present which could be classified according to the stigmas observed as resulting from contact with the rheumatic virus.

Of the so-called positive cases there were 68 (60.7 per cent) in all; 36 (32.1 per cent) were in the probable rheumatic group, and only 8 in the doubtful column.

TABLE V

SAMPLE OF LARGER TABLE (112 HEARTS); THIS INCLUDES AGES 41-50 ONLY

				CARDIAC VALVES THICKENING				VASCULAR				PERIVASCULAR		
NUMBER	AGE AND SEX	HT. WT.	HISTORY RHEUM. FEVER	FUSION COMMIS.	AORTIC	MITRAL	TRICUSPID	ARTERITIS "RHEUM."	FIBRINOID NECROSIS	ELASTIC TISSUE ALTERATION	ASCHOFF BODY	FIBRINOID "SWELLING"	CELLULAR INFILTRATION	POSITIVE + PROB. P DOUBT. D
	41-50													
22258	F 45	440	–	–	+	+ ch	+	++	++	++	–	++	++	+
S-4202	M 50	420	N.R.	–	–	±	–	+	+	++	–	+	+	D
S-4159	M 49	250	N.R.	+	–	+	–	++	++	+++	+	++	++	+
S-4431	M 48	325	N.R.	–	–	+	+	+	++	++	±	+	++	P
S-5113	M 50	450	N.R.	–	–	+ ch	–	++	++	+++	+	++	+	+
24286	F 43	300	N.R.	–	–	+ sl.ch	–	++	++	++	+	+++	+++	+
22040	F 43	410	N.R.	–	–	–	–	++	++	+++	+	+++	+++	+
25008	F 43	300	N.R.	–	–	–	–	+++	+++	++	+	++	++	+
S-5170	F 45	325	Sore throats	–	–	+	–	++	+++	++	–	+++	+	P
S-5188	M 47	325	N.R.	–	–	–	–	+	+++	+	–	++	+	P
25655	M 41	310	N.R.	–	–	ch	–	++	+++	++	±	+++	++	+
26397	F 47	300	N.R.	–	–	+	–	++	++	+++	+	+++	+	+
24416	M 45	600	–	–	–	+	–	+	++	++	+	++	+	+
26545	M 49	470	–	–	–	–	–	–	+	++	–	+	++	P
S-6081	F 45	150	N.R.	–	–	–	–	++	++	+++	–	++	+	+
S-6429	M 50	500	N.R.	–	–	+	+	++	+++	+++	+	+++	++	+
S-6397	F 46	300	–	–	–	+	+	+++	++	+++	+	++	+++	+
S-6083	M 50	450	N.R.	–	–	+	–	+++	++	+++	+	++	+++	+

It would require too much space to publish a complete table of 112 cases. We have therefore selected the 18 cases which fall in the 41 to 50 age group as a sample for detailed presentation (Table V). There were 10 males and 8 females. The weight of the heart is not pertinent to the present study. In only one specimen was there slight fusion of the aortic commissures, and in only one instance was there aortic cusp thickening. The mitral valve was the seat of minimal thickening in 12 hearts, or 66.6 per cent. The tricuspid was similarly involved in 4 instances. The chordae tendineae were thickened in 4 hearts, in each case in connection with the mitral leaflets. All of the rheumatic stigmas were well represented in this group except in the second case, S-4202, which is considered doubtful as regards rheumatic taint. There are 13 cases in the positive group, four in the probable, and only one in the doubtful. In 10 specimens (55.5 per cent) Aschoff bodies were found. In 2 cases sub-Aschoff nodules were present, and in 6 there were none.

The main lesions found at autopsy in each of the 112 cases were recorded on our master table. Careful analysis failed to reveal any essential relationship to the problem in hand, and therefore the autopsy diagnoses are not included in Table V. It was thought that some relationship might exist in the large group with general arteriosclerosis and hypertension, especially among those with coronary occlusion. An analysis of this group, however, revealed a slightly lower percentage of cases of coronary occlusion than was found among the autopsies at the Los Angeles County Hospital for the year 1939-40.

COMMENT

The facts presented here are interesting, but their significance is difficult to evaluate. Until our knowledge of the etiology of rheumatic fever is more complete, the interpretation of the so-called rheumatic stigmas must be more or less hypothetical. It is well established that rheumatic fever is closely associated with hemolytic streptococcus infections.[8, 14, 15] Coburn[14] reported recently that in cases of infection with hemolytic streptococci without later development of rheumatic fever, the antistreptolysin titer rises no later than two weeks after the initial infection, but, in cases of developing rheumatic fever the titers rise in the third week and remain high as long as the disease remains active. The relationship of rheumatic carditis to allergic-hyperergic inflammation has been widely accepted.[5, 8, 9, 10, 12] Coburn[14] has suggested that rheumatic fever develops in persons who, because of hereditary and environmental deficiencies, are unable to react to infections with hemolytic streptococci in the usual way. Their immune response to the primary infection is inadequate, with the result that the cells of the reticuloendothelial system become sensitized. Recurrent infections with these organisms produce in such persons the symptoms and the allergic-hyperergic tissue changes known as rheumatic fever. The majority of

the population are relatively immune to these organisms, and therefore are not subject to rheumatic infections. The hemolytic streptococci referred to by Coburn are those of the A group of Lancefield.

According to a recent survey by Paul,[15] children in institutions for rheumatic heart disease tend to develop exacerbations of rheumatic carditis two or three weeks after upper respiratory infections caused by hemolytic streptococci. Jones and Mote[16] report that, of 271 observed recurrences of rheumatic fever, 67 per cent were associated with infections of the respiratory tract, two-thirds of which were symptomatic sore throats. Of the first rheumatic attacks, 58 per cent were preceded by infections of the upper respiratory tract. These attacks of carditis would appear to be allergic-hyperergic reactions to the products of the hemolytic streptococci.

Assuming, with Coburn[14] and others, that the hemolytic streptococcus is the etiologic agent in rheumatic fever, one may logically explain the rheumatic stigmas found in the papillary muscles and immediate vicinity of the cardiac valves by assuming that they are allergic phenomena which result from repeated streptococcal infections of tonsils, pharynx, and sinuses in persons who are able to respond in the usual way. Such repeated infections may selectively affect the cardiac valves and produce mild inflammatory responses which result in minimal thickenings of the valve edges. Certainly in the patients who develop rheumatic fever the valves are involved early and often severely. The inflammation also spreads to the myocardium but is usually most evident near the valves. In the immune patient, changes characteristic of rheumatic infection can be found, but as a rule only in close proximity to the valves. The papillary muscles, to which the chordae tendineae are attached, appear to be most affected.

Possibly the reaction is not as specific as we have indicated. Swift and his associates[8] point out that a variety of streptococci have been isolated from blood cultures and the lesions of acute rheumatic fever. Animals sensitized to one strain of streptococcus have shown marked hypersensitivity to that particular strain, but have also been quite sensitive to other strains, as well.

If later investigations demonstrate a specific organism other than the streptococcus in rheumatic fever, the explanation offered above is still pertinent. Whatever the organism may be, it probably gains entrance through the nose or tonsils, for the majority of rheumatic infections follow upper respiratory disease.[16] The so-called stigmas of the rheumatic virus discussed in this paper may nevertheless represent manifestations of allergy to repeated upper respiratory infections in persons who are relatively resistant. Just as the pleural scars at the apices of the lungs are the "vaccination marks" which indicate immunity to tuberculosis, so the minimal valvular lesions and microscopic hyperergic changes in the heart muscle indicate immunity to rheumatic fever resulting from previous subclinical infections.

SUMMARY

1. Of 124 hearts studied, 112 were free of valvular lesions as commonly understood. The remaining 12 specimens presented gross lesions of chronic rheumatic endocarditis or subacute bacterial endocarditis, or both. This smaller group constituted our controls.

2. Among the larger group of 112 hearts, minimal thickening of the mitral valve leaflets was observed 74 times (66.0 per cent). Slight thickening of aortic cusps and tricuspid leaflets was present much less often. The chordae of the mitral valve were thickened in 42 cases, or 37.5 per cent.

3. The various microscopic rheumatic stigmas were studied in blocks from the papillary muscles of the left ventricle and in some cases from blocks passing through each of the valves. All of the stigmas ,(arteritis, fibrinoid changes, elastic tissue alterations, Aschoff bodies, and infiltration with histiosytes) were abundantly present.

4. Aschoff bodies were found in thirty-three (29.5 per cent) instances and Aschoff-like collections in an additional 34 hearts (30.3 per cent).

5. "Positive," healed, minimal rheumatic infection was diagnosed 68 times (60.7 per cent), "probable," healed, minimal rheumatic infection, 36 times (32.1 per cent), and 8 specimens were called doubtful.

6. There was a history of rheumatic fever or chorea in 9 of the 12 patients in the control group. The rheumatic stigmas were abundant in all but one case. This patient had syphilitic aortitis, in addition to chronic rheumatic valvular disease and bacterial endocarditis.

CONCLUSIONS

1. About 90 per cent of the hearts studied revealed stigmas of rheumatic infection in the myocardium in close proximity to the mitral valve.

2. These lesions are believed to be the result of allergic-hyperergic responses to recurrent upper respiratory infections with the rheumatic virus in persons who are relatively immune.

3. The hemolytic streptococci would seem logically to fit the role of rheumatic agent under the conditions proposed. We have presented no direct evidence that this is true.

4. The present study indicates a widespread distribution of the rheumatic virus, comparable perhaps to that of tuberculosis or poliomyelitis. As a corollary to this, the greater percentage of the population is immune to the virus of rheumatic fever, just as it is to tuberculosis and poliomyelitis.

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STUDIES WITH THE BALLISTOCARDIOGRAPH IN ACUTE CARDIAC INFARCTION AND CHRONIC ANGINA PECTORIS

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HERETOFORE, the reported clinical studies with the ballistocardiograph[1-6] have been widespread surveys to gain experience with the common deviations from the normal. This, our first study of a specific disease by this method, deals with the coronary type of heart disease and includes studies made both during the acute stage after cardiac infarction and in cases of chronic angina of effort. There have been very few studies of the amount of the circulation in these conditions,[7, 13] probably because many of the patients are too ill to permit the application of the older cardiac output methods. Therefore, we planned to estimate the amount of the circulation in many cases of coronary heart disease and hoped to be able to gain information beyond the scope of the methods which are routine in most hospitals.

Since 1937, about 1,600 ballistocardiograms have been made on subjects at the University Hospital, chiefly from the medical wards. Among these were 106 records on 55 patients with angina pectoris or cardiac infarction. All of these patients had been examined by one or both authors, and most of them had been directly under their care. To avoid unconscious bias, all the records were reviewed and classified by one of us (F. C. W.) without knowledge of their ballistocardiograms. The comparison of the clinical aspects, as observed by one author (F. C. W.), with the ballistocardiograms, as analyzed by the other author (I. S.), and the conclusions that can be drawn therefrom, form the subject of this paper.

The results indicate that profound abnormalities of the amount of the circulation, sometimes accompanied by alterations of impact form, are commonly, but not invariably, found in coronary heart disease. The data show that these abnormalities may develop and recede during the acute period after cardiac infarction, but that they are found with greater frequency and severity in cases in which there is a long history of angina pectoris.

METHODS

Apparatus.—The principles and construction of the ballistocardiograph, the apparatus used to secure records of the heart's recoil and the blood's impacts, have been described.[1] Nothing is required of the patient except that he lie relaxed and motionless on the table, so that the method is well adapted for the investigation of ill persons.

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Taking records.—Estimations of blood pressure and all ballistocardiograms were taken while the subjects lay on their backs in the horizontal position, after a rest period of at least fifteen minutes, and never within two hours of a meal. The acutely ill patients were brought to the ballistocardiograph room in their beds and lifted directly from the bed to the table. Electrocardiograms were occasionally taken simultaneously with the ballistocardiograms by projecting the string's shadow on the same film, but more frequently they were taken in the usual manner within a few days of the corresponding ballistocardiograms.

Reading the records.—Typical examples are given in Figs. 2 and 5, and it is well to precede the details of record analysis by several general statements.

Since any movement made by the patient affects the record, artifacts are common, and only the constantly repeated features deserve any attention.

With reservations to be discussed, the amplitude of the systolic waves is related to the absolute value of the cardiac output, but large persons naturally have a greater amount of circulation than small ones, so that the decision concerning what is normal rests on the relation of the cardiac output to the size of the person. Also, older persons, even though they are healthy, give smaller impacts than their juniors. Moreover, if the impact form is abnormal, there are data to support the belief that the cardiac output may be larger than the amplitude suggests. Therefore, the record of one person may not necessarily be directly comparable with that of another, but records obtained on the same person at different times are directly comparable.

The decision concerning normal ballistic form.—The first step in the analysis of any record is to decide whether the form is normal or abnormal; diagrams of both kinds are shown in Fig. 1. The normal can be recognized at a glance, and attention should be concentrated on the I and J waves, for, from their areas, cross-hatched in the figure, the cardiac output is calculated. Sharp and well-defined I and J waves have been found in all the records on healthy persons, and in a great majority of those on patients. They are caused by the recoil from, and the impacts of, the blood moved by systolic ejection. The other features of normal records on healthy persons are less constant. Just before ejection an upward H wave usually occurs, and, especially if the rate is slow, this may be preceded by a complex of small waves which, since they resemble the impacts after isolated auricular contractions in heart block, are probably caused by motion of blood imparted by auricular contraction. But this feature is not well marked in all normal subjects, nor is this part of the record always flat in auricular fibrillation, so that other factors must enter in. During diastole a series of small waves occur; these are attributed by Hamilton[8] to standing waves in the aortic blood, for they coincide with aortic pressure waves. We have data to support this interpretation in some cases. Always much smaller than the normal systolic complexes, these waves vary in amplitude in healthy persons and are almost absent in some.

The size of the normal complexes always varies with the phases of respiration; it increases during inspiration and diminishes during expiration.

The common types of abnormality can easily be recognized by comparison with the diagrams of Fig. 1, but it must be kept in mind that those shown are extreme examples, and that complexes whose shape lies between such forms and the normal are encountered more frequently.

Analysis of records with a normal form.—When the form was normal, cardiac output was calculated by the area method.[2] No claim has ever been made that the value obtained is highly accurate; indeed the absolute accuracy of all cardiac output methods is unknown. Nevertheless, results in individual cases are readily reproducible, the characteristics of normal records are well known, and we have no doubt that the major deviations from the normal which are found in so many cases are significant.

The values for cardiac output per minute, per unit of body weight, will be expressed as percentage deviations from the average normal; the normal limits are

±22 per cent. When thus expressed, the application of the correction of Cournand, et al.,[9] which adjusts for the underestimation of the size of the living aorta, from tables based on data obtained at necropsy, does not alter the result because both normal and abnormal values are changed proportionally.

One of the aims in estimating cardiac output is to gain information concerning the heart's work and so obtain evidence of its strength or weakness. Because the pulmonary pressure is unknown, only the work of the left ventricle can be estimated, and, leaving out the velocity factor, which is negligible in most resting subjects, this work is approximately equal to the mean blood pressure, in mm. Hg, times the specific gravity of mercury, 13.6, times the cardiac output. Normal standards for left ventricular work per minute per pound of body weight have been compiled from a series of healthy persons, 57 men and 48 women, between the ages of 20 and 40 years. Using Cournand's correction,[9] the ventricular work per minute per pound of body weight of healthy young adults averages 36.0 Gm. meters for men and 34.0 Gm. meters for women; the standard deviations are 5.2 and 5.6 gram meters, respectively. Combining these values, we obtain an average normal of 35.0 Gm. meters per minute with the usual statistical limits of normal, i.e., twice the standard deviation, 30 per cent above and below this figure. Data obtained by the ethyl iodide method on 31 normal persons yielded almost identical values.[12]

It must be noted that the standard deviation of the left ventricular work is about one-third larger than that of the cardiac output of healthy persons. This means that the work of the heart among healthy persons scatters over a wider range than the cardiac output. Therefore, the normal limits for work are considerably wider than those for output, and larger differences are required before the work of any patient can be considered abnormal.

Analysis of records with an abnormal form.—In 17 of the 106 records, the form was so abnormal that we were unable to estimate cardiac output with enough confidence to give it a numerical value. Records *b*, *c*, *d*, *f*, and *g* of Fig. 2 are examples of the abnormal types encountered. Most of the 13 abnormal records resembled *b* or *c*, and in these the amplitude was so low that a subnormal cardiac output may be properly inferred, although an exact value should not be given. Nevertheless, the bulk of our discussion will be centered about the 89 records of normal form.

In a few records, as *e*, Fig. 2, the abnormality is confined to a part of the respiratory cycle. In these we have usually calculated cardiac output from the largest and smallest normal systolic complexes, and we do not believe that the error of so doing would be large. Again, the amplitude of such records is always so small that only the degree of the "*hypokinemia*" could be in error.

The terms "*hyper-*" and "*hypokinemia*"[6] will be used to express the corresponding abnormalities of the amount of the resting circulation under the conditions of our tests. For convenience of expression, the left ventricular work of resting patients under the conditions of our experiments will often be referred to as the cardiac work, without further qualification.

Criteria used in classification of patients.—The criteria which Wood employed were such that doubtful cases of coronary heart disease would be excluded from our series, even though some real cases were probably also eliminated.

The diagnosis of *chronic* coronary disease was based upon: (1) The presence of typical angina of effort for at least several months; (2) our knowledge that a definite cardiac infarction had occurred previously; and (3) the presence of typical electrocardiographic signs of healed anterior or posterior infarction, together with a history suggesting former cardiac infarction. A rough classification of the severity of the condition was made by dividing the cases into mild, moderate, and severe on the basis of exercise tolerance, as ascertained by questioning, not by direct testing.

The diagnosis of *acute* coronary occlusion was based upon the occurrence of an attack of pain followed by either (1) the typical electrocardiographic pattern of one of the recognized types of cardiac infarction, or (2) progressive changes in the electrocardiogram which were not the result of drug administration or any other obvious cause except infarction. The cases were classified as mild, moderate, or severe according to the degree and duration of the fever and leucocytosis which followed the attack, the severity and duration of the pain, the diminution of the blood pressure, and the occurrence of shock or failure.

Selection of cases.—In aortic regurgitation, as part of the blood expelled in systole reenters the heart in diastole, the amount of the circulation cannot be estimated from the ballistocardiogram. Therefore, such cases were not studied, and the well-known group with angina pectoris secondary to syphilitic aortitis is not represented in our data.

RESULTS

Abnormalities of Ballistic Form in Coronary Disease.—Records showing abnormal ballistic forms were encountered in 17 instances. Most of these were obtained from patients with symptoms of over three years' duration, although, because of an acute attack shortly before, some of them are classified as acute in Table I.

The characteristic "late downstroke" type, diagrammed in Fig. 1*b*, was encountered infrequently. The record of R. J., Fig. 2*g*, who suffered from biliary tract disease and later from pain characteristic of angina pectoris during effort, is a classic example of this type, but we have no similar case in our series. Forms intermediate between this and the normal, i.e., shallow I waves and retarded J peaks, were seen occasionally.

The "late M" type is diagrammed in Fig. 1*c*, and similar records on patients with coronary disease were reproduced in a previous publication.[2] Attributed to a ballistic imbalance of the two sides of the heart, we had wondered if this abnormality would be found to be characteristic of cardiac infarction, but this has not proved to be so. The expectation based on theory has been weakened by the realization that, for anatomic reasons, movement of the blood in the systemic arteries plays a far larger part in the genesis of impacts than movement in the pulmonary system.[14] Also, our larger experience has not borne out our early observations, partly because we have become more strict in interpreting the records. Those like the third record of patient H. B., shown in Fig. 2, *j3*, we might have previously accepted as the late M type, but the second apex of the M is small and occurs after systole is over, so that it is probably an after-vibration, i.e., a large "L" wave. It is the lack of the second after-vibration, the "N" wave, which makes the record look unusual. Typical "late M" tracings (Fig. 2*f*) are certainly to be found in coronary heart disease, but they occur infrequently. Since in many cases of cardiac infarction only a small proportion of the total ventricular muscle is found to be damaged at necropsy, it seems reasonable that the blood might be ejected with a normal velocity curve in many resting subjects with small lesions, especially if cardiac output has diminished.

A third type of abnormality is the "early M" type, shown in Fig. 1*d;* the first limb of the M is an exaggerated H wave. Records of this type are sometimes hard to distinguish from "late M" records without additional evidence of the exact position of systole, which we obtained by a simultaneous electrocardiogram whenever we were in doubt. The second record of H. G., Fig. 2, *d2,* is a conspicuous example of this type, and we have three other records in cases of coronary disease which resemble it. Although less conspicuous examples occur in hypertension, the extremes of this abnormality have all been found in records from patients with recent infarction.

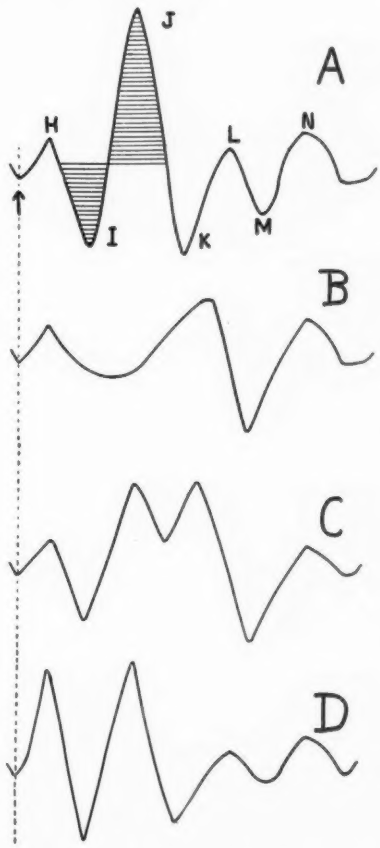

Fig. 1.—Diagrams of the normal ballistocardiogram and extreme types of the abnormalities of form, aligned by the arrow and dotted line at the beginning of ventricular systole, as shown by the electrocardiogram.

A. Commonest type of normal record. The wave areas used to estimate cardiac output are crosshatched. The letters are those given to the corresponding peaks and valleys.

B. The "late downstroke" type. The downstroke late in systole is the most conspicuous feature of these records.

C. The "late *M*" type. The *first* apex of the M corresponds to the J wave in the normal record. This form is interpreted as a combination of the two preceding records, *A* and *B.*

D. The "early *M*" type. The abnormality is an exaggeration of the *H* wave of the normal record, and the *second* apex of the *M* is the *J* wave.

Fig. 2.—Ballistocardiograms from patients with chronic coronary heart disease, illustrating the abnormalities of form, contrasted with the normal, and records obtained in a single case over a period of years. The records are reproduced three-fifths their original size.

To aid readers in interpreting the records the time of the beginning of ejection of blood from the heart has been marked by a line underneath the records. In records *d* 1 and 2, and *e*, the placing of this line was assisted by an electrocardiogram which was recorded on the same film as the ballistocardiogram. There was little doubt about the placing of ejection in the other records, except *B*, in which the amplitude is so small and the form so confused that systole cannot be identified with confidence.

a; A normal record for comparison with the abnormal records below, taken on the senior author, aged 46 years, height 6 feet, weight 185 pounds.

b; Record of E. K., aged 51 years, height 5 feet, weight 119 pounds. Coronary occlusion eleven years before, angina after effort since that time. Blood pressure, 186/98, heart normal in size by orthodiagram. Anginal attacks now occur while she is in bed. Given paravertebral alcohol injection the day after this record was taken. A ballistocardiogram one week later showed no improvement. Note the small amplitude of the ballistocardiogram.

c; E. Q., aged 62 years, 5 ft. 1 in., 140 lbs. Blood pressure 175/92. Angina after effort for at least six years. The story was a little suggestive of acute infarction four days before this examination, when she had a changing electrocardiogram, but it was not diagnostic. Note the tiny ballistic amplitude.

d; H. G., aged 55 years, 5 ft. 10 in., 164 lbs., blood pressure 110/70. First record, four days after anterior infarction, with characteristic electrocardiogram. At this time there was auricular fibrillation with a ventricular rate of 148. Note the large amplitude and the varying ballistic forms that are always seen in auricular fibrillation. Second record, eight weeks after infarction, blood pressure, 112/70, normal sinus rhythm. Note the early M shape of ballistic record. This patient died of liver abscess and septicemia five months later. Necropsy confirmed the diagnosis of infarction.

e; S. K., aged 54 years, 5 ft. 5 in., 174 lbs., blood pressure, 114/86. Record obtained four months after posterior infarction, with characteristic electrocardiogram changes. The course during the acute period was not unusually severe, but the patient had recurring pain after effort and even in bed, and was still bedfast when this record was made. Note the small ballistic amplitude and the abnormality of the J wave in the smaller complexes of the respiratory cycle, where the J peak is flattened, notched or retarded. The larger complexes are normal in form.

f; J. B., aged 49 years, 5 ft. 1 in., 135 lbs., blood pressure, 118/80. Probably posterior infarction two years before, with angina after effort thereafter. Anterior infarction eight weeks before this record, recovering slowly. Note "late M" form over most of the respiratory cycle.

g; R. J., aged 64 years, 5 ft. 9 in., 173 lbs., blood pressure 112/75. Formerly, chronic cholecystitis and cholelithiasis. Gall bladder and stones removed seven years before this record. History of attacks of substernal pain after effort for the preceding two months. Electrocardiogram practically normal. Note the late downstroke type of ballistic record.

h; I. H., aged 57 years in 1937, 5 ft. 8 in., 170 lbs. This man, examined as a healthy person in 1937, later developed angina and died of infarction (see text). Note small amplitude, especially in the smaller complexes.

i; K. V., aged 74 years in 1937, 5 ft. 3 in., 120 lbs. This woman, examined as a healthy person, developed angina four years later. She is living and active at present, aged 79 years.

j; H. B., aged 60 years, 5 ft. 5 in., 167 lbs. First record in 1937, when supposedly healthy. Note low amplitude. The rapid camera speed makes this record appear more different from the following than it actually is. Second record, 1938, six weeks after posterior infarction, mild course. Note low amplitude and flattening of J waves in smallest complexes. Third record, 1940, working steadily and effectively as an orderly, admits angina after unusual exertion. Note larger amplitude. The vague M shaped appearance is misleading; the second apex of the M is in diastole, the systolic form is normal. Fourth record in 1941. Angina occurs on less effort. He is now unable to work effectively and has lost his job. Note smaller amplitude than previous record.

k; K. N., aged 33 years, 6 ft. 2 in., 208 lbs., blood pressure, 116/75. He had myocardial infarction with severe symptoms about two years before this record was made, and almost died of embolism; femoral embolectomy was required. At the time of this test, clinical recovery was practically complete and he was working hard. At time of writing, one year later, he has had no further trouble. Note that the ballistic record is completely normal.

l; E. D., aged 60 years, 6 ft., 173 lbs., blood pressure, 105/70. This man had myocardial infarction with mild symptoms about one year before this record was taken. No residual symptoms were admitted. Note that the ballistocardiogram is entirely normal. At time of writing, three years later, he is working hard at the practice of medicine and has had no further trouble.

In confirmation of the observations of Tennant and Wiggers,[10] one of us (Wood) has often noted that, when a dog's coronary artery is ligated, the area of the heart which is deprived of its normal circulation soon begins to bulge with each systole. Such a weak spot in the cardiac wall near the apex, bulging when systole begins, should cause a displacement of the center of mass of the heart's blood downward until ejection took place. The recoil from this movement would throw the body headward and cause the ballistic H wave to be increased in

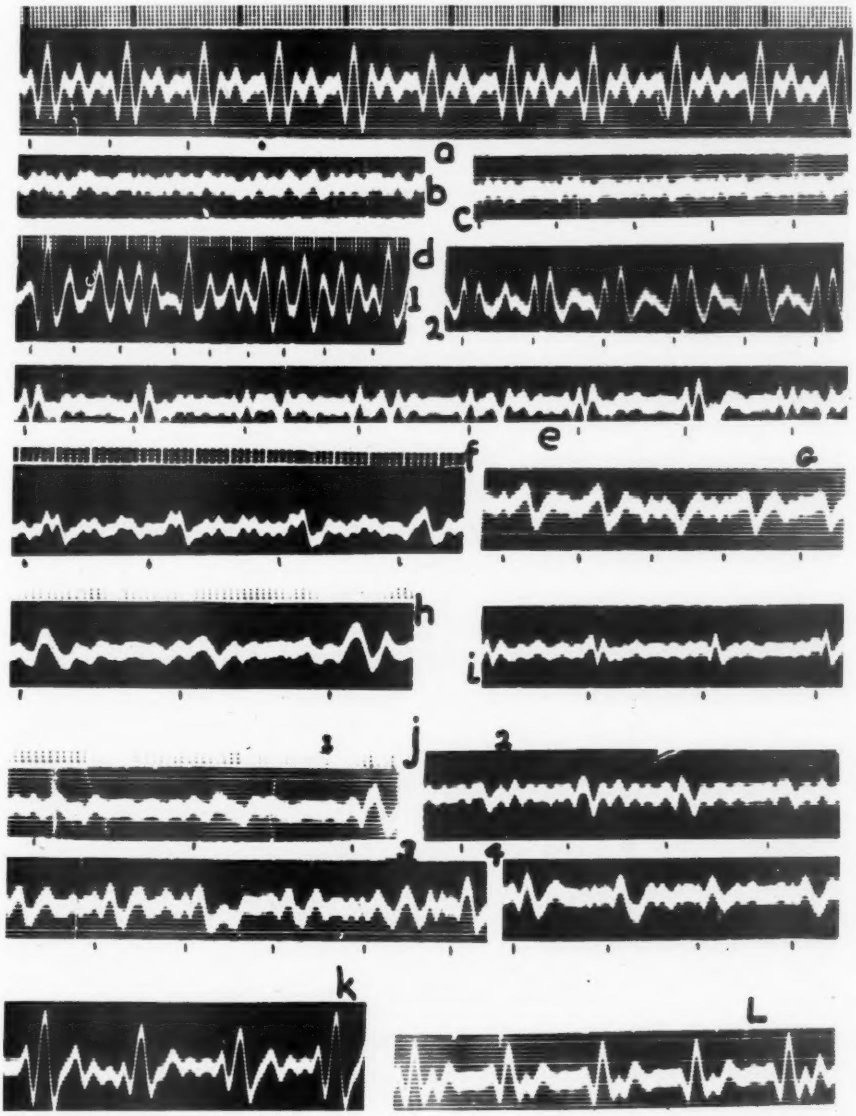

Fig. 2.—(*For legend see opposite page.*)

size. We have not performed animal experiments, however, to support or disprove this speculation.

A fourth type of abnormality was encountered most frequently in this study. In it the whole ballistocardiogram is so greatly reduced in amplitude that the individual waves are hard to identify, and the details of form are correspondingly uncertain. The record of patient E. K., Fig. 2*c*, is of this type, and we have found similar records in nine other cases.

In addition to these extreme types, we have numerous records in which an abnormality of impact form was confined to the smaller complexes of the respiratory cycle; the record of S. K., Fig. 2*e*, is an example.

When the records were of the early M type we calculated cardiac output from them in the usual manner, but when the form is of the late M, or late downstroke, type, the ordinary criteria for estimating cardiac output may not be applied. Rather than use criteria concerning whose accuracy we have little knowledge, we have not given a numerical value to the cardiac output estimated from any of these abnormal records, so that their data do not appear in the charts. Nevertheless, the amplitude was usually so small in these cases that we feel justified in the belief that the circulation was very subnormal. Nothing has been found among these abnormal records which is inconsistent with the results to be reported quantitatively.

Estimations of Cardiac Output and Work in Coronary Heart Disease.—The statistical analysis is given in Table I. Unfortunately the number of cases is too small to permit fine distinctions.

TABLE I

STATISTICS IN ACUTE CARDIAC INFARCTION AND CHRONIC ANGINA PECTORIS

		NO. OF CASES	NO. RECORDS IN ABNORMAL FORM	CARDIAC OUTPUT		L. V. WORK	
				MEAN DEVIATION FROM EXPECTED NORMAL	STANDARD DEVIATION ABOUT THE MEAN	MEAN DEVIATION FROM EXPECTED NORMAL	STANDARD DEVIATION ABOUT THE MEAN
Acute							
Severity	Mild	9	2	-33%	5%	-20%	10%
	Moderate	12	3	-17%	3%	-17%	6%
	Severe	6	2	-17%	9%	-20%	10%
Chronic							
Severity	Mild	6	0	-13%	8%	0%	12%
	Moderate	6	1	-43%	7%	-25%	11%
	Severe	16	4	-35%	4%	-32%	4%

In acute coronary occlusion the average work of the heart is not significantly correlated with severity, as judged by the symptoms. To our surprise, in mild cases there was a smaller average cardiac output than in patients with more severe symptoms. When the data from mild cases were compared with those of the moderate group, this difference was significant, but, when compared with the smaller number of severe

cases, no statistical significance was apparent. But it must be remembered that complicating factors, such as pain, apprehension, and fever, enter into the results in acute infarction. Also, some patients whose disease was classified as mild because the acute attack produced few symptoms at rest had suffered from severe angina of effort for many years. Such patients may have had a larger proportion of their myocardium destroyed than was the case among those who had infarction without any antecedent history of coronary disease. Also, data obtained both soon after infarction and during convalescence are included in the analysis. The group lacks homogeneity, and it is not surprising that the statistics are uninforming.

The results in the chronic group were more in accord with expectations, for the average resting cardiac work was directly related to exercise tolerance. The difference between the cardiac work when exercise tolerance is little reduced, and the values obtained when it is moderately or greatly reduced, are highly significant, and this statement applies to the output, also. The difference between the values among those with moderate, and those with great, reduction of exercise tolerance does not attain statistical significance.

Considering the data as a whole, one sees that the averages of both work and output are far below normal in coronary disease, and they are more reduced in the chronic than in the acute stages. Of the two, output is more reduced than work. But, as is shown by the standard deviations, the scattering of the data is considerable. The averages, therefore, do not merit too much attention, and the analysis of individual cases gives a more interesting picture.

Studies in Acute Cardiac Infarction.—By good fortune we examined patient E. D. about two weeks before, as well as after, cardiac infarction and the results are shown in Fig. 3. Syphilis, never adequately treated, had been diagnosed three years before, but there were no clear signs of aortic regurgitation, and the diagnosis of arteriosclerotic heart disease was preferred. Symptoms strongly suggesting angina of effort had been present for a month, and it was thought that cardiac infarction might be in the offing; this led to admission to the hospital, where a ballistocardiogram was secured. Two weeks later he had a severe attack of substernal pain which lasted about twenty-four hours and was not relieved by nitrites. Fever, leucocytosis, and more rapid sedimentation of erythrocytes followed, and typical electrocardiographic evidence of recent anterior infarction developed. Six days after this incident his blood pressure was lower, and a ballistocardiogram showed that the circulation had also diminished; the left ventricular work per minute had declined 33 per cent. Estimations made during the next few weeks showed that the changes in cardiac output and blood pressure were small and in opposite directions; the work remained about the same. The smallest circulation was found during the fourth week, when the only estimation below the lower normal limit was obtained; at this time

the blood pressure had recovered somewhat. After this, uneventful clinical recovery was accompanied by increased circulation, but the original blood pressure was not regained, and, at discharge, the left ventricle was calculated to be doing 20 per cent less work than before the infarction.

The observations in this case are consistent with those in most other cases; the records and data of one such case are given in Fig. 4. In Fig. 3 are charted the values for cardiac output and work in the twenty-

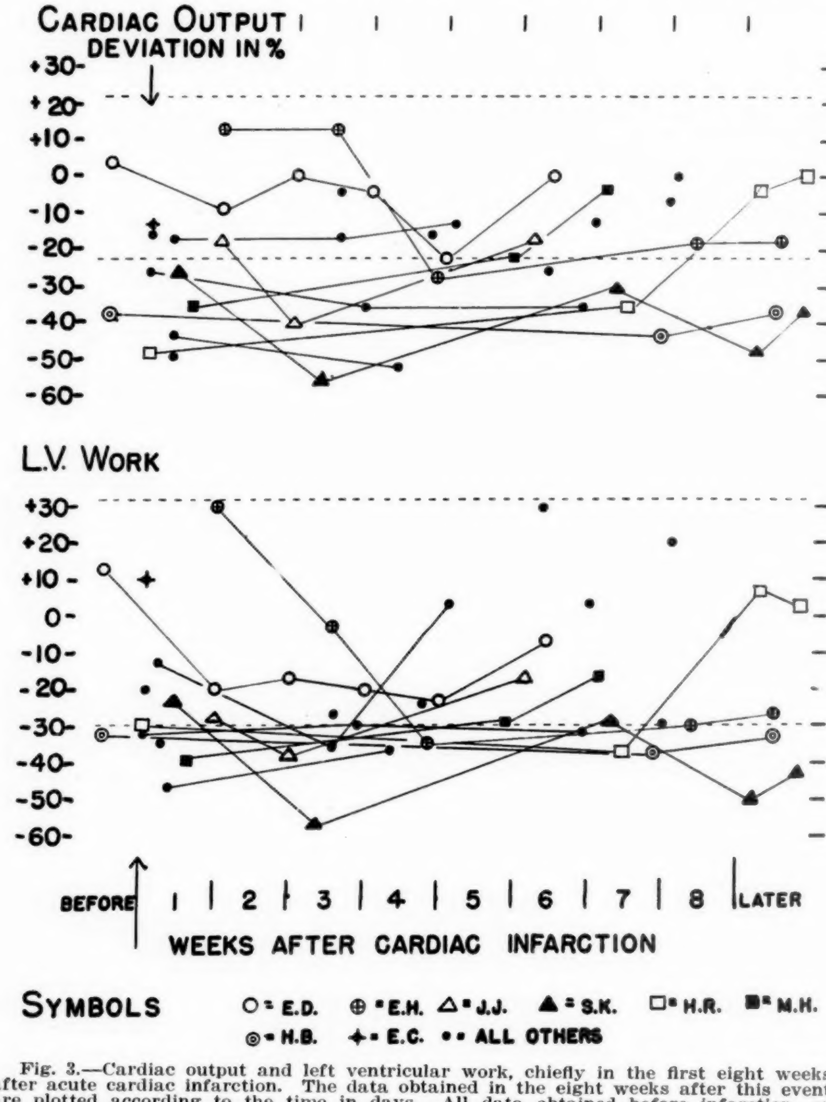

Fig. 3.—Cardiac output and left ventricular work, chiefly in the first eight weeks after acute cardiac infarction. The data obtained in the eight weeks after this event are plotted according to the time in days. All data obtained before infarction, or later than the eight weeks after it, are plotted without regard to time. Values obtained from the same subject are connected by solid lines.

The horizontal dotted lines indicate the statistical limits of the cardiac output and left ventricular work of normal subjects, and are placed at a distance of twice the standard deviation from their mean. The values of 95 per cent of healthy persons will be found within the dotted lines.

one cases in which we obtained ballistocardiograms of normal form during the eight weeks after cardiac infarction. Obviously, both cardiac output and work tend to diminish during the first four weeks; this trend was absent only in those cases in which we found unusually low values at the first test; in these the diminution may have already taken place.

After the fourth week, clinical improvement was accompanied by a return of the circulation and work toward normal, and all, except two patients, were discharged in reasonably good condition. Patient E. C. died during the first week, and S. K., after restoring his circulation and work part of the way toward normal, failed to hold the gain. The clinical course of the latter corresponded to these observations, for angina on very little effort confined him to bed on discharge, and, when readmitted two months later, he was no better.

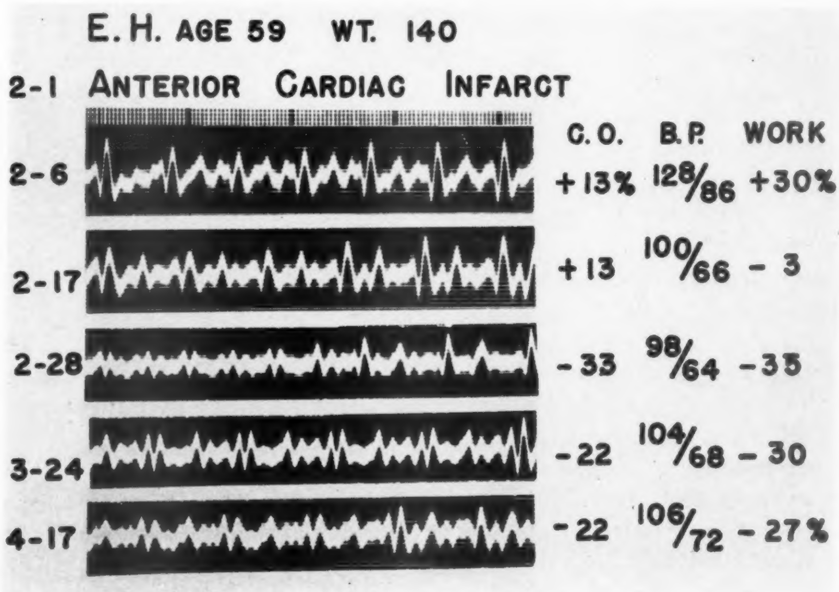

Fig. 4.—Ballistocardiograms obtained on the same subject during the acute stage of cardiac infarction, with the calculated cardiac output, blood pressure, and left ventricular work. The records have been reduced to three-fifths actual size. The time record at the top applies to all; the longest interval is one second.

On the Course of Chronic Coronary Heart Disease.—The records of a patient who was followed for 4 years are reproduced in Fig. 2*j*. H. B., a hospital orderly, was first examined in 1937 in the general roundup of supposedly normal persons during the study which determined the normal standards. To our surprise the cardiac output was far subnormal, although the subject admitted no symptoms at the time. A typical, although mild, attack of posterior cardiac infarction occurred a little over a year later, and the second record was obtained six weeks after this event, just before he was ready for discharge from the hospital.

The circulation was still far below normal at that time. The patient made a good clinical recovery, lighter work was found for him, and he worked steadily for the next few years, although he had angina after unusual effort. The third ballistocardiogram, taken 20 months after the infarction, showed a little improvement in the circulation, but it was still far from normal. The gain was not maintained, angina appeared after less and less effort, and fifteen months later he was discharged as unable to do the work required. At this time the circulation was again found to be extremely subnormal.

Several points about this experience are illuminating. First, an abnormality of the circulation was discovered early in the course of the disease before symptoms were admitted, and well over a year before acute infarction was diagnosed. Second, after recovery from the acute symptoms the cardiac output was lower, but very little lower, than before. Third, some recovery took place, and, finally, this recovery was not maintained. Our other evidence on these points will now be taken up.

The Circulation Early in Coronary Heart Disease.—During 1937 and 1938, two hundred healthy persons of all ages were examined on the ballistocardiograph as part of the study to determine the normal standards. Fifty-six of these persons were over 50 years of age. Eleven of these persons, all men but one, proved to have hypokinemia. The after-histories of these eleven patients are of great interest because five of them developed clear evidence of coronary heart disease in the years which followed.

Most of these subjects were either physicians or other professional persons employed in the Medical School, and none of them admitted symptoms when tested in 1936 to 1937. Nevertheless, the obvious conclusion that we had detected an abnormality of the circulation before the development of symptoms of coronary disease was weakened by the discovery that one subject had failed to inform us of a mild coronary attack, accompanied by electrocardiographic changes suggesting a small infarct, which had occurred two years before. Reticence about such ailments is very characteristic of physicians, and it is conceivable that the others might have had more trouble than they admitted; moreover, those who were not physicians may have failed to interpret their sensations properly. Thus we are not certain that a ballistocardiographic abnormality preceded the appearance of symptoms, but it did precede "recognized," or at least "admitted," symptoms in several subjects.

F. D., aged 69 years, with a circulation of –35 per cent in 1937, had mild angina on considerable effort about a year before his death in an accident at the age of 73 years. F. G., aged 59 years, who failed to admit evidence of infarction in 1935, had a circulation of –39 per cent when first examined in 1937. At that time he appeared to be in good health, but he has had at least one small cardiac infarct since. He made a good recovery and is working actively at present.

K. V., a "healthy" woman, who had a subnormal circulation (Fig. 2*i*) when examined in 1938 at the age of 74 years, developed mild, transient, substernal pain on rapid stairclimbing at the age of 78 years. The attending physician believes this to be angina. The patient continues to be extremely active for her years; she works for hours at a time in her flower garden, and the condition is evidently extremely mild.

I. G., aged 57 years, was also examined as a healthy person in 1937. At that time his circulation was –35 per cent. The course of the case was complicated, and the patient, a physician, was not communicative about his troubles. A renal calculus was removed at operation in 1940. An infection with Brucella abortis incapacitated him for over a month in 1941, and he never altogether recovered his health. Anginal attacks were first observed by the attending physician about three months before death, in 1942. The last illness began with pneumonia, complicated later by empyema which was surgically drained. He was rallying from this when he died quite suddenly. Necropsy showed an infarct of the lateral wall of the left ventricle which was judged to be several days old. There was marked, widespread arteriosclerosis, including the coronaries.

Although coronary heart disease has developed in a considerable percentage of older persons with subnormal circulations, it has also developed in subjects in whom we failed to demonstrate any abnormality of the circulation. C. N., a man, aged 48 years when examined in 1937, had a circulation of –13 per cent; this is well within normal limits, although below average normal. He had typical cardiac infarction in 1941. The course was mild and he made a good recovery. Six months later his circulation was –22 per cent, at the lower limit of normal.

It should also be noted that the circulation of E. D. (Fig. 3) was normal during the period of premonitory symptoms that preceded a cardiac infarct.

The Circulation and Cardiac Work Late in Chronic Coronary Disease.—In Fig. 5 are plotted all the data obtained in the chronic stages of coronary heart disease. Included in this group are all patients who had had infarction in the past, irrespective of whether definite angina followed it, and all cases of angina pectoris, irrespective of whether infarction was diagnosed previously; but all values obtained within eight weeks after infarction have been omitted. Multiple values obtained in any one year have been averaged; the results have been plotted according to the duration of the symptoms.

The cardiac outputs of these patients (Fig. 5) are below normal in the great majority of instances. There seems to be a slow trend downward as the disease advances.

When the left ventricular work is studied, the proportion of the cases within the normal range is larger, almost one-half; this is the result, in

part, of the inclusion of three cases of hypertension. Many such patients, when the heart is hypertrophied and not failing, have a higher basal cardiac work than normal persons. The fact that the work of such hearts, after the development of coronary heart disease, is within normal limits does not mean that the work is not less than it was before coronary disease manifested itself. To judge such cases we need a separate "normal" standard for cardiac work in cases of hypertension, and the data are not yet sufficient to supply it.

In spite of this difficulty, the tendency for the work of the heart to diminish as the disease advances is quite obvious from the data in Fig. 5.

Anginal-like Attacks With Biliary Tract Disease.—Four of our patients who were thought to have angina pectoris also had biliary tract disease. Their data have been given an identifying mark in Fig. 5, and have not been included in Table I. Each had a long history of attacks of substernal pain on exertion, relieved by nitrites. In three patients the electrocardiogram showed little or nothing abnormal, in one it showed the signs of former anterior infarction. In all four cases, the ballistocardiogram indicated a profound depression of the circulation. In each there was evidence of gallbladder disease, and each had been subjected to an operation on the biliary tract, at which time abnormalities were discovered and corrected. In spite of this, attacks of substernal pain persisted in two of the cases, although in one (S. L.), exercise tolerance was improved after the operation. In the third case, anginal-like pain began several years after the operation. The fourth patient had had no pain since her operation, but she was last seen only a month later and had taken no exercise.

The diagnosis of angina might be challenged in these cases, and, indeed, there is never any objective proof of this diagnosis, even at necropsy. But the extraordinary abnormality of the circulation, namely, –39 per cent, –52 per cent, and –48 per cent, respectively, in three of the cases, and the abnormal form of the fourth ballistocardiogram (Fig. 2*g*) indicated a definite abnormality of the cardiovascular apparatus in these patients. That this abnormality may have been directly related to the biliary tract disease was suggested by the reproduction of anginal-like pain and circulatory depression when fluid was injected into the common duct in one case.[5] Evidently we are learning more about the association of angina with biliary tract disease, an association which has long been recognized by clinicians.

DISCUSSION

Physiologic Considerations in Acute Myocardial Infarction.—

Adaptations to the disability: Although normal values for cardiac output were found frequently during the first week after infarction, at some time between the second and the fifth week subnormal values were present in almost all of our cases. Enough experience is available to convince us that simple rest in bed, on a restricted diet, will not cause

changes of this magnitude. Thus the hypokinemia may well be an adaptation to the cardiac disability which results from infarction.

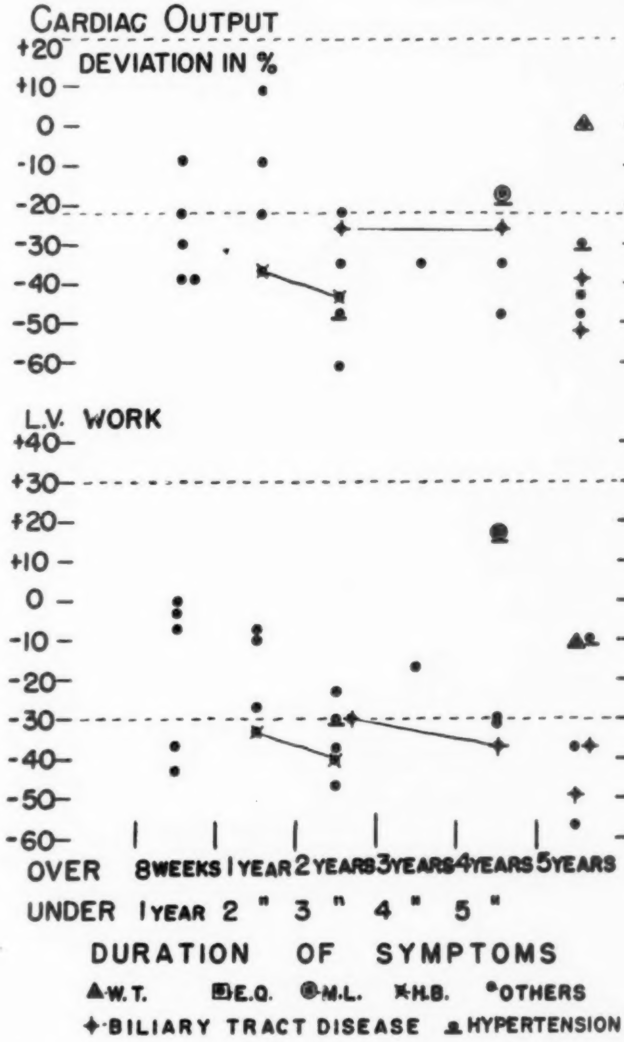

Fig. 5.—Cardiac output and left ventricular work in chronic coronary heart disease, except in the eight weeks after infarction. The horizontal dotted lines represent the limits of normal, as in Fig. 3.

As far as one can see, the best physiologic compensation for infarction of the left ventricular wall would be to reduce the work of the left ventricle. This would diminish the metabolic demands of the tissue about the infarct, where the circulation is reduced but not abolished, and so might permit this area to survive until the development of collateral circulation and the canalization of the thrombus could restore its blood supply. Theoretically, the work of the left ventricle could be reduced

by diminishing the output of blood or the resistance to this output, i.e., the general blood pressure, but there are theoretical disadvantages in so doing. Diminution of circulation has long been believed to favor intravascular clotting, so that compensation by this means would favor the formation of mural thrombi when the endocardium was involved, and so lead to embolism. One might also suppose that a sluggish circulation would favor extension of the coronary thrombus, but one of us (Wood) has examined the necropsies in a large number of cases of cardiac infarction without obtaining evidence that extension of this thrombus had ever occurred.

To diminish the work of the heart by reducing the blood pressure courts trouble in another direction, for the diastolic pressure is the main driving force of the coronary circulation, and to decrease it too much might put that circulation in jeopardy at a time when its adequate maintenance is vital.

Evidently, patients with cardiac infarction must steer a course between dangerous alternatives, and not all of them take the method which, in the light of present knowledge, seems most promising.

The results obtained in one case (H. G., omitted from Fig. 3 because of abnormal ballistic form) differ from our other experiences. These records are reproduced in Fig. 2 *d*. These records, taken simultaneously with an electrocardiogram when cardiac pain was present four days after the acute cardiac infarction, show auricular fibrillation with a ventricular rate of 130. Although any estimate of the circulation is rendered less accurate by the varying abnormalities of ballistic form which always occur with auricular fibrillation, there is no doubt that the cardiac output and work were far above the normal for a man of this age and weight. Normal rhythm was resumed spontaneously, and a second record was obtained five weeks later. This ballistocardiogram is characterized by extraordinary H waves of the early M type. Again the circulation, although smaller than before, was still above normal, but the work had diminished to a level within the normal range. Six months later this patient died of liver abscess and septicemia; necropsy demonstrated the old infarct in the anterior part of the left ventricle.

In this case, during the acute symptoms, the work of the heart was increased. Factors which might stimulate the circulation after cardiac infarction are pain, apprehension, and fever. These might explain the hyperkinemia in the first of these tests, but not in the second, when convalescence was well established. Therefore, one can hardly deny the possibility that other factors were at work.

The question why, in this case, the work of the heart was increased is related to the question why, in other cases, it was not decreased. E. C., our only patient to die during the first week, gave normal values for both cardiac output and work when tested three days before death. A large infarct on the posterior surface of the left ventricle was demon-

strated at necropsy. One wonders why more rest was not provided for this heart. This patient, however, had suffered from diabetes and moderate hypertension for many years. The blood pressure after the infarction was within normal limits, so that considerable reduction in the work of the heart may have taken place before our test was made.

Studying Fig. 3, one wonders why it took several weeks for some patients, e.g., E. H., to reduce their work to a minimum. No answer can be given to this question, but it should be recalled that the maximal physiologic adaptation to the lower oxygen supply at high altitudes requires several weeks. Perhaps when the tissues lack oxygen because of diminution of the circulation, time is required for full adaptation.

Another factor in this slow reduction of work is the behavior of the blood pressure. That blood pressure diminishes after cardiac infarction is well known, and no detailed description of our data is required. Subnormal values were found soon after the infarction in some cases; in others a much more gradual decline occurred. This reduction did not always run parallel to the diminution of cardiac output, and so was not the result of change in the latter. It should be considered another adaptive mechanism.

Relation of cardiac work to pain: The case of H. G., cited previously, and other examples in Fig. 2 provide many instances in which pain after infarction subsided as the cardiac work diminished. This raises the question of a casual relationship, such as is commonly believed to exist in simple angina of effort. It seems proper to suppose that cardiac work is a factor in the pain of infarction, but other factors must operate also. The disappearance of pain in some cases was not accompanied by any diminution of work that we could measure. Destruction of sensory nerves in the involved area, development of collateral circulation, and other processes of healing doubtless play a part in the relief of pain.

The work of the heart and the electrocardiogram: Since exercise will sometimes bring out electrocardiographic changes suggestive of coronary disease which are absent at rest, we sought for a correlation between the cardiac work and the changes in the electrocardiogram which took place during the subsidence of symptoms of infarction. We were unable, however, to demonstrate that any constant relationship existed.

Physiologic Considerations in Chronic Angina of Effort.—When our results are arranged according to the duration of the symptoms of coronary disease (Fig. 5), they give a viewpoint concerning the course of this disease. The general picture looks much like that of the closely related peripheral vascular diseases, i.e., a chronic course with a slow trend downward which may be hastened by acute vascular occlusions but also may be interrupted by periods of considerable recovery of function.

Our data also show that patients with angina may be divided into three main groups: Those with normal circulation, those with hypokinemia, and those whose pattern of cardiac ejection, as demonstrated by distorted ballistic form, is abnormal. We have examined our data

to discover whether or not these physiologic differences were accompanied by any variations in the clinical manifestations.

Cases of angina in which the circulation is normal: We have encountered two patients who have had angina pectoris for over five years whose cardiac work was normal when they were at rest, and, in one, both cardiac output and work were normal. The latter (W. T.), a man, 63 years of age, had had angina for 14 years, and remained employed as a guard all this time. In 1940, he developed very mild congestive failure, but recovered promptly on rest and digitalis. At present his heart is not enlarged as seen roentgenographically, his blood pressure is normal, and his electrocardiogram shows little abnormality. Certainly this patient has done very well.

The other patients with chronic angina whose circulations are well within the normal range, omitting those at the lower limit of normal, include a man, K. N., aged 33 years, who made an excellent recovery from a severe infarction about two years before; at present he is working hard and has no angina after any ordinary effort. Also in this group is D. B., a man, aged 60 years, who at the time of examination seemed to have completely recovered from the effects of a mild attack of infarction two years before, and, at present, three years later, is working hard and in good condition. Another with a normal circulation was M. F., a man, aged 65 years, who was still in the first year of his symptoms, and more incapacitated by nervousness than by angina. Finally, there was M. L., a woman with moderate hypertension in the fifth year of her symptoms, who came to the hospital for relief of a pain which was probably not cardiac in origin. Nevertheless, while in bed on the ward, she had an attack of substernal pain which was thought by the intern, who observed it, to be angina caused by excitement. If this is the correct interpretation, this is the only patient with angina and a normal circulation whose angina was not very mild.

Cases of angina in which there was marked hypokinemia: Fig. 5 shows data from fifteen patients whose circulation was –30 per cent or less. Nine of these had anginal attacks while in bed in the hospital. Four others developed congestive failure during the course of their disease. One, I. Z., who could walk only a city block without pain when this examination was made, has since grown worse, and her ballistocardiogram is now abnormal in form. The patient who seemed in best condition had cholelithiasis, and there was some doubt about the diagnosis of angina.

Cases of angina in which the ballistic forms were abnormal: Among these were found our most seriously ill patients. One died a week after the record was taken, and another within a few months. One patient's angina was so severe that paravertebral nerve block was performed to give relief. Another, who also had diabetes and hypertension, was having attacks of angina without exertion. Another, I. Z., whose

ballistic form became abnormal as her exercise tolerance diminished, has been mentioned. Still another, E. Q., has had angina for ten years, recently complicated by a uterine carcinoma.

Summary.—When the patient has a normal circulation the disease tends to be mild; patients with hypokinemia but normal ballistic form tend to be more incapacitated; and those with an abnormal ballistic form are by far the most seriously ill.

The Ballistocardiogram Compared With the Electrocardiogram.—We have been so often asked to compare these two methods of examination that a few words on this subject seem in order if we limit the discussion to our experience with coronary heart disease.

As anyone with knowledge of the fundamentals of these instruments would expect, they measure entirely different properties of the heart, and each can detect types of abnormality which escape the other. For example, in the first week after cardiac infarction the electrocardiographic abnormalities are at a maximum, whereas the ballistocardiograph reveals nothing abnormal in some cases. This situation is often reversed. Although they are not the only examples, the three patients with anginal-like attacks and also biliary tract disease, previously discussed, whose electrocardiogram showed little or nothing and whose ballistic records were profoundly abnormal, may be recalled.

Apparently the electrocardiogram most easily detects localized lesions when they are in a position to upset the balance of the electrical potential which is obtained by leading from the body surface. But, as is shown by the small and inconsistent changes which occur in the electrocardiogram after exercise, changes of function which affect the heart as a whole are not well detected. On the other hand, the ballistocardiogram, which is tremendously influenced by physiologic changes, such as exercise, will easily detect conditions affecting the heart as a whole, whereas the localized lesions, probably involving only a small fraction of the heart muscle, may not disturb function enough to influence records of resting subjects.

It must always be remembered, however, that the fact that the circulation is subnormal is not valid evidence that the heart is diseased. A major interest of workers with the ballistocardiograph is the study of the noncardiac types of circulatory abnormalities which are at present not detected by any other objective clinical method. Only when the form is abnormal does the ballistocardiogram give unqualified evidence that the heart itself is functioning abnormally, and abnormalities of form are found in only a small proportion of records of cardiac cases.

Clinicians must learn to view measurements of the amount of the circulation in much the way that they now regard estimates of blood pressure. One must not expect to diagnose the anatomic lesions found at autopsy, although the ballistic records may add to the evidence from which the presence of such lesions may be inferred. The function of the ballistocardiogram is to estimate how such lesions are affecting the ability of the heart to pump the blood and the result of treatment upon this function.

The Utility of the Ballistocardiogram in the Diagnosis of Coronary Heart Disease.—Some mention must be made of the utility of the ballistocardiogram in the diagnosis of coronary heart disease, for, although final conclusions are hardly warranted, tentative conclusions are. In the acute period immediately after infarction, the ballistocardiogram is too variable to give much support to this diagnosis. In the examination of patients with chronic coronary disease, it is much more valuable.

We have found only one case of chronic coronary heart disease in which the circulation was above the expected normal average; that patient, K. N., a young man, might be said to have almost completely recovered from a previous infarction. Thus, if the circulation is above the average normal, the chances of chronic coronary disease would seem to be remote.

In the diagnosis of angina pectoris, so much depends on the patient's statements that one is often misled by his failure to mention former illnesses or his misinterpretation of important symptoms. Additional evidence of an objective character is often very welcome. The ballistocardiogram provides this in the great majority of instances, either by disclosing an abnormal impact form, or by giving evidence of subnormal circulation. Other pathologic processes may cause similar ballistic changes, but these can usually be easily identified. A subnormal circulation in a patient over 50 years of age without obvious signs of organic heart disease, cardiac arrhythmia, congestive failure, endocrine disease, or hypertension, who is not convalescent, moribund, or in shock, should lead one to suspect coronary heart disease. The patients with essential hypokinemia or neurocirculatory asthenia, who also have a subnormal circulation without any other abnormalities that are demonstrable by the clinical methods in ordinary use, are usually younger persons.

Besides giving aid in diagnosis, the ballistocardiograph permits calculation of the cardiac work, and therefore the measurement of its strength or weakness by a method more direct than the usual clinical techniques. Weakness of the heart may manifest itself in more than one way. In one type the work per minute diminishes; in another it is maintained, but only by drawing on the cardiac reserve. In previous investigations[11, 12] we studied both the size of the heart and its work; cardiac enlargement out of proportion to performance per beat was found to be characteristic of patients who had had, or were threatened with, congestive failure. In these the work per minute was often normal. In coronary heart disease the weakness was not of this type, an observation that we have confirmed in this investigation, for we have roentgenologic evidence of the size of the heart in the great majority of our cases. As is well known, cardiac hypertrophy and dilatation are not characteristic of such cases; perhaps the widespread coronary damage prevents the employment of these reserves. In a majority of the cases of coronary disease, the weakness is manifested by a reduction

of the basal work per minute. Our evidence suggests that the extent of this abnormality is a measure of the severity of the disease.

SUMMARY

Ballistocardiograms were made 106 times on 55 patients with coronary heart disease.

In the acute period after infarction the circulation may be either normal or below. If normal, it tends to diminish, and usually reaches a minimum below the normal limit between the third and fifth week. Later, recovery sets in. The left ventricular work, as calculated from the cardiac output and the blood pressure, follows a generally similar course.

In chronic coronary heart disease, with angina of effort, the circulation is subnormal in the great majority of cases, and the ballistocardiogram provides objective evidence to support the diagnosis.

Abnormalities of the form of the ballistocardiogram are frequently encountered in coronary heart disease, usually when the patient has greatly reduced exercise tolerance.

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THE ANATOMIC CAUSE OF ELECTROCARDIOGRAPHIC CHANGES IN VIRUS MYOCARDITIS OF RABBITS

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FOR many years there has been a clinical concept of the debility of the cardiovascular system resulting from or accompanying a number of acute infectious diseases. Of these, perhaps diphtheria, influenza, and scarlet fever are followed most commonly by instability of the circulatory system that is evidenced mainly by subjective symptoms, but occasionally by abnormalities of heart rate or blood pressure and transient alterations in the electrocardiogram.[1-3] For these there has never been any well demonstrated anatomic cause. A variety of other diseases, chief among which are many of the virus infections of man, are also said to be accompanied by myocarditis. Measles, mumps, smallpox, yellow fever, psittacosis, certain pneumonias, and acute infections of the upper respiratory tract have been implicated.[1] In most instances the evaluation of the disturbed cardiac condition rests solely on clinical and electrocardiographic observations, but even in those cases in which necropsy is done there is seldom the possibility of correlating the electrocardiograms with the inflammatory lesion in the myocardium.

This situation has resulted in two points of view. On the one hand there is the opinion that the subjective symptoms of cardiovascular incompetence and the transient deviation of the electrocardiogram from the normal pattern are the result of some toxic influence which alters the dynamics of the heart without causing any morphologic change, whereas, on the other hand, there is the more conservative opinion that true inflammatory lesions exist in the myocardium of the abnormally functioning heart.

In rheumatic fever, also, although the cause of this disease remains obscure, the cardiac involvement which occurs in the early and acute stages is often manifested, among other ways, by changes in the electrocardiogram. The correlation of these changes with morphologic alterations in the heart is almost invariably precluded by the recovery of the patient, or at least by his continued survival and the evolution of the acute lesion into the so-called "chronic rheumatic heart."

A method of elucidating these obscure states and the possibility of explaining them by visible anatomic alterations, if only by analogy, has recently arisen in the demonstration of the various cardiac lesions which occur in rabbits during the course of virus infections. It has been shown[4, 5] that rabbits inoculated subcutaneously or intratesticularly with a variety of filtrable viruses develop cardiac lesions which,

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when the animal has been subjected to suitable preparatory procedures, are severe and extensive. The lesion is predominantly a myocarditis, regardless of the nature of the infecting virus.

The present paper consists of an electrocardiographic study of some of these experimentally induced virus infections, both in the initial stage of the acute infection and in the stages of recovery, made in an attempt to show that the abnormality in the electrocardiogram is dependent upon structural changes and visible lesions in the heart.

METHOD

Virus myxomatosum, pseudorabies virus, vaccine virus, virus III, and Shope's tumor strain and Andrewes' inflammatory strain of the fibroma virus may produce a specific myocarditis in rabbits when inoculated peripherally.[5] The frequency and severity of the myocarditis are markedly increased if the animal is subjected to some procedure which is designed to produce a transitory alteration in the dynamics of the circulation. Since the simplest and most successful of these procedures is the intravenous injection of approximately 50 c.c. of 20 per cent gum acacia solution immediately before the intratesticular inoculation of the virus, this method was used in the present investigation to produce the cardiac lesions.

Virus III[6, 7] and Andrewes' inflammatory strain of the fibroma virus[8, 9] were the infecting agents of choice because neither of these viruses is sufficiently virulent to kill; yet infection with each results in a high incidence of cardiac involvement.

TABLE I

CORRELATION OF ACUTENESS OF INFECTION,* ELECTROCARDIOGRAPHIC ABNORMALITIES, AND MYOCARDITIS IN RABBITS INOCULATED WITH VIRUS III

RABBIT NUMBER	TIME OF ELECTRO-CARDIOGRAM†	FEVER AND ORCHITIS	ELECTROCARDIO-GRAPHIC ABNORMALITIES	MYOCARDITIS
1	2-9	Present	Marked	Marked
2	2-9	Present	Slight	Moderate
3	2-9	Present	Absent	Marked
4	2-9	Present	Absent	Moderate
5	3-13	Present	Marked	Moderate
6	3-13	Present	Marked	Moderate
7	3-13	Present	Marked	Marked
8	3-13	Present	Absent	Marked
9	14	Present	Moderate	Moderate
10	14	Present	Moderate	Absent
11	14	Present	Absent	Absent
12	14	Present	Absent	Absent
13	14	Absent	Absent	Absent
14	14	Absent	Absent	Absent
15	14	Absent	Absent	Absent
16	14	Absent	Absent	Slight
17	14	Absent	Absent	Slight
18	14	Absent	Absent	Slight
19	14	Absent	Absent	Absent
20	20	Absent	Absent	Absent
21	20	Absent	Absent	Slight
22	20	Absent	Absent	Slight
23	24	Absent	Absent	Slight
24	24	Absent	Absent	Slight
25	24-26	Absent	Marked	Marked

*Acuteness of infection was judged by the presence of fever and orchitis, recognizable in the living animal. It is the presence or absence of these signs at the time of obtaining the electrocardiogram which is tabulated.

†The numerals indicate the number of days after inoculation at which the electrocardiogram was obtained. Two numerals separated by a hyphen indicate that serial records were made during that period.

All of the rabbits were young males weighing between 1,500 and 2,500 grams. They were not selected as to breed or strain and were acquired from several sources.

Approximately 50 c.c. of 20 per cent gum acacia solution in distilled water or physiologic saline were injected into the marginal ear vein of each of 46 rabbits. Immediately thereafter 25 of these rabbits were inoculated in each testis with 0.5 c.c. of a 5 per cent suspension of virus III infected testis and 21 were similarly inoculated with 0.5 c.c. of a 5 per cent suspension of inflammatory fibroma infected testis. The suspensions which were used for inoculation were prepared by grinding an infected testis, excised during the acute stage of the disease, under sterile conditions, with sand and a small amount of 0.85 per cent salt solution in a mortar. The resultant paste was then diluted to 5 per cent with additional salt solution.

In all of the experimental animals, successful infection was evidenced by an elevation of temperature and obvious enlargement and induration of the inoculated testis.

The method of obtaining electrocardiograms has been described in detail in a preceding publication.[10] It consisted of using the three conventional limb leads, and, in addition, a left chest and a right chest lead. Tracings were made daily or on alternate days on 15 rabbits in the virus III infected group and on 7 rabbits in the fibroma infected groups during the stage of the acute infection, which was considered to be the period from 2 days after inoculation through the ensuing 9 to 14 days. Electrocardiograms were taken on the remaining 10 rabbits in the virus III group at intervals of 14, 20, or 24 days after inoculation, and, on the remaining 14 rabbits in the fibroma group, 14, 24, 31, and 37 days after inoculation (Tables I and II).

TABLE II

CORRELATION OF ACUTENESS OF INFECTION,* ELECTROCARDIOGRAPHIC ABNORMALITIES, AND MYOCARDITIS IN RABBITS INOCULATED WITH THE INFLAMMATORY FIBROMA VIRUS

RABBIT NUMBER	TIME OF ELECTROCARDIOGRAM†	FEVER AND ORCHITIS	ELECTROCARDIOGRAPHIC ABNORMALITIES	MYOCARDITIS
1	3-10	Present	Absent	Marked
2	3-10	Present	Absent	Moderate
3	3-10	Present	Absent	Absent
4	4-14	Present	Absent	Marked
5	4-14	Present	Absent	Slight
6	4-14	Present	Absent	Slight
7	4-14	Present	Absent	Absent
8	14	Absent	Absent	Absent
9	14	Absent	Absent	Slight
10	14	Absent	Absent	Slight
11	24	Absent	Absent	Slight
12	24	Absent	Absent	Moderate
13	24	Absent	Absent	Marked
14	24	Absent	Absent	Absent
15	31	Absent	Absent	Slight
16	31	Absent	Absent	Slight
17	37	Absent	Absent	Slight
18	37	Absent	Absent	Slight
19	37	Absent	Absent	Slight
20	37	Absent	Absent	Slight
21	37	Absent	Absent	Absent

*See footnotes to Table I.

Tracings taken on 9 of the virus III infected rabbits before the induction of the disease, together with the previously published series of electrocardiograms[10] on normal rabbits, served as controls. Any possibility of an effect on the electrocardiogram brought about by the large intravenous injection of acacia alone was precluded by the fact that many of the experimental animals which had received acacia, as well as virus, showed no abnormality in the electrocardiogram. The

absence of effect of acacia alone was further confirmed in 3 rabbits by tracings taken both during the injection and at 2- to 6-day intervals thereafter.

The rabbits in both groups which were studied electrocardiographically during the early and acute stages of the disease were killed on the day the last tracing was made in order to have close correlation between the anatomic condition of the heart and the evidence of its functional state. Those animals which were studied at a later period, when all clinical manifestations of infection had subsided, were frequently not killed until several days after the last tracing had been made. It seemed probable that, after the long interval following inoculation, any cardiac lesions which might have persisted would be in the nature of a fibrous scar which could change but little.

The hearts were fixed intact in Zenker's solution and then trimmed by longitudinal section into blocks, which included all four chambers and valves. This method, described in detail in a previous paper,[4] makes possible the histologic study of all parts of the heart in their normal relationship.

RESULTS

In the normal rabbit electrocardiogram[10] there are marked spontaneous changes in the form, voltage, and direction of some of its components. Transient reversal of the T wave in Leads I or III and in the chest leads is frequently observed. T_2, however, is constantly upright, so that inversion of T_2 can be used as a criterion of significant abnormality. Slight RS-T segment deviations, never exceeding one millimeter, are frequently encountered. The P-R interval never exceeds 0.10 sec., and the duration of the QRS complex never exceeds 0.04 second. Abnormal rhythms are not seen in the normal animal. Hence prolongation of the P-R interval beyond 0.10 second and the inception of abnormal rhythms can likewise be regarded as criteria of significant dysfunction.

The results of the experiments with virus III are shown in Table I. It is evident at once that significant changes in the electrocardiogram occur, as a rule, only when a marked anatomic alteration is present in the myocardium, but that both minor and severe lesions may exist without bringing about any noteworthy alteration in the tracing. Rabbits 1 to 8, which were inoculated with active virus, developed well-marked and widespread necrotizing and inflammatory cardiac lesions, as well as definite clinical evidence of disease. Five of these 8 animals also had significant alterations in their electrocardiograms. The most serious of these was transient, complete auriculoventricular heart block (Fig. 1, rabbit 7), or transient RS-T segment deviation of more than one millimeter.

The photomicrographs (Figs. 2 and 3) of the heart of the animal (rabbit 7) on which such tracings were obtained illustrate the type of lesion in the myocardium. The morphology and localization of these cardiac lesions have been described in considerable detail in a previous publication.[4] In brief, they consist of local or diffuse areas of necrosis and disappearance of muscle fibers, accompanied by an infiltration of large mononuclear leucocytes, lymphocytes, and occasional polymorphonuclear leucocytes. There is a variable amount of fibrous tissue re-

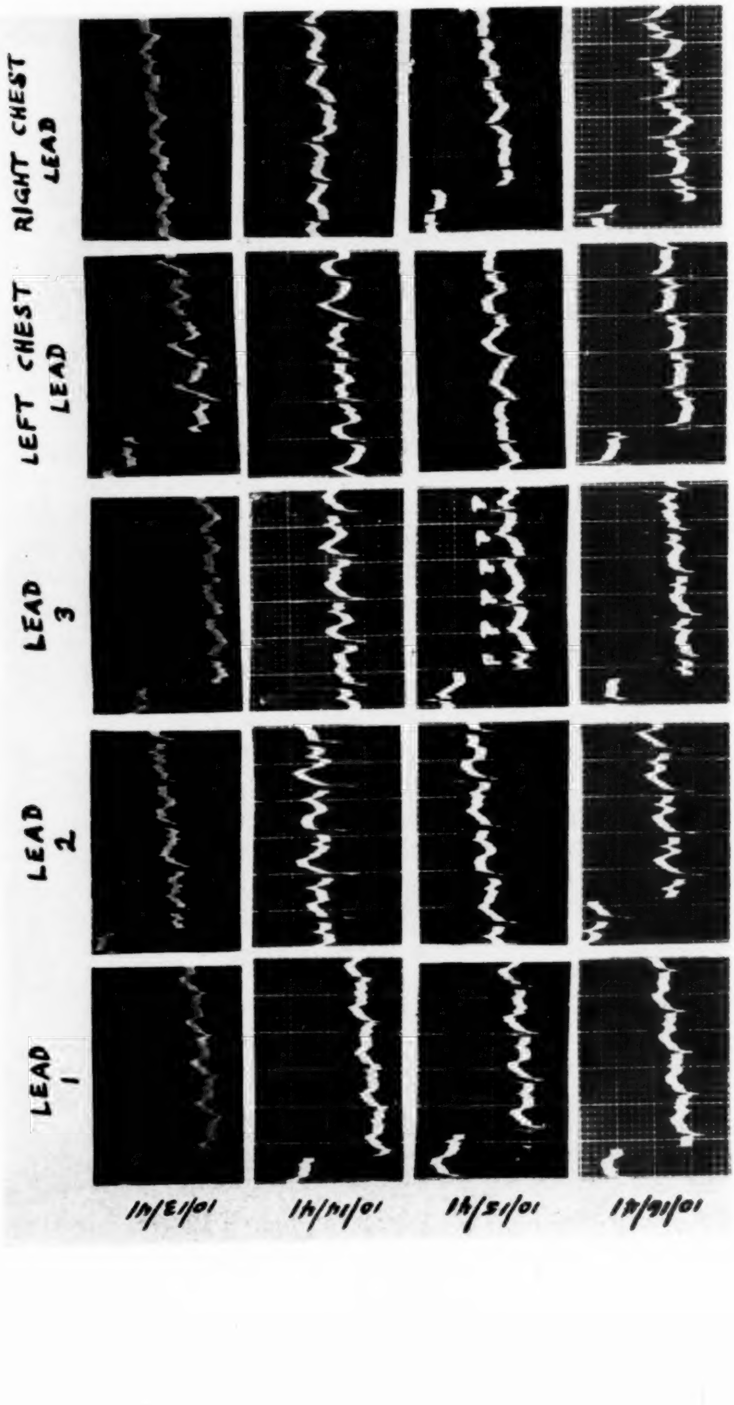

Fig. 1. *(See continuation and legend on opposite page.)*

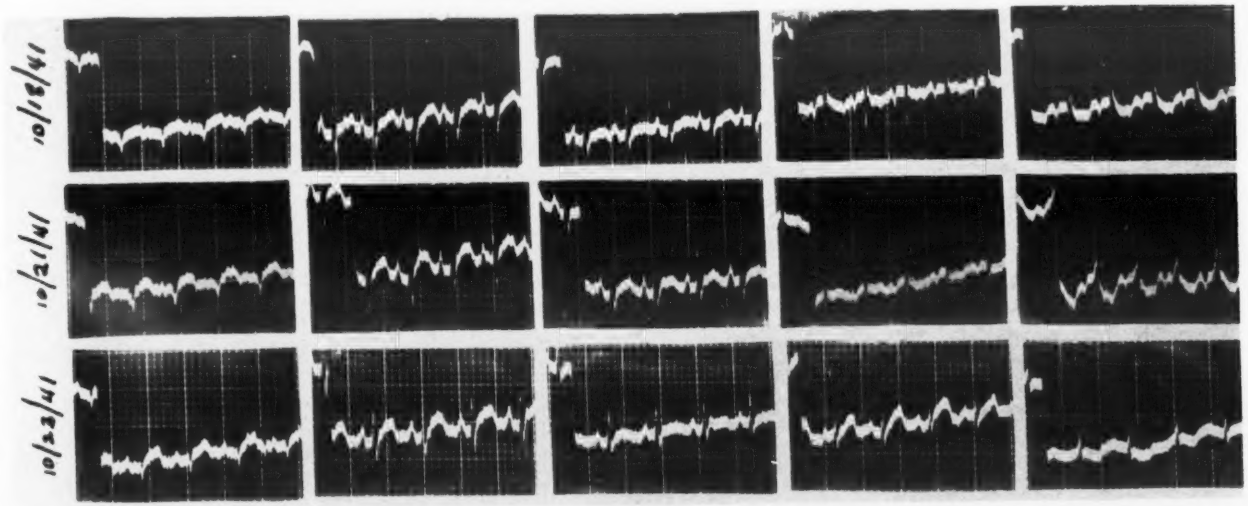

Fig. 1.—Sequential five-lead electrocardiogram taken from rabbit 7 during the acute stage of experimental virus III infection. The tracings, taken 4 days (10/14/41) and 5 days (10/15/41) after inoculation, show bizarre complexes which, on careful caliper examination, are found to be characteristic of complete auriculoventricular heart block. On the following day (10/16/41) there is a return to normal sinus rhythm. The transient T-wave reversal in the left chest lead is not significant, for it may occur in the normal rabbit.

placement. Intranuclear inclusion bodies which are typical of the virus may be found in the mononuclear cells, the fibroblasts, or the muscle cells.

It is noteworthy, however, that severe myocarditis may be present, as in rabbits 3 and 8, without any electrocardiographic evidence thereof.

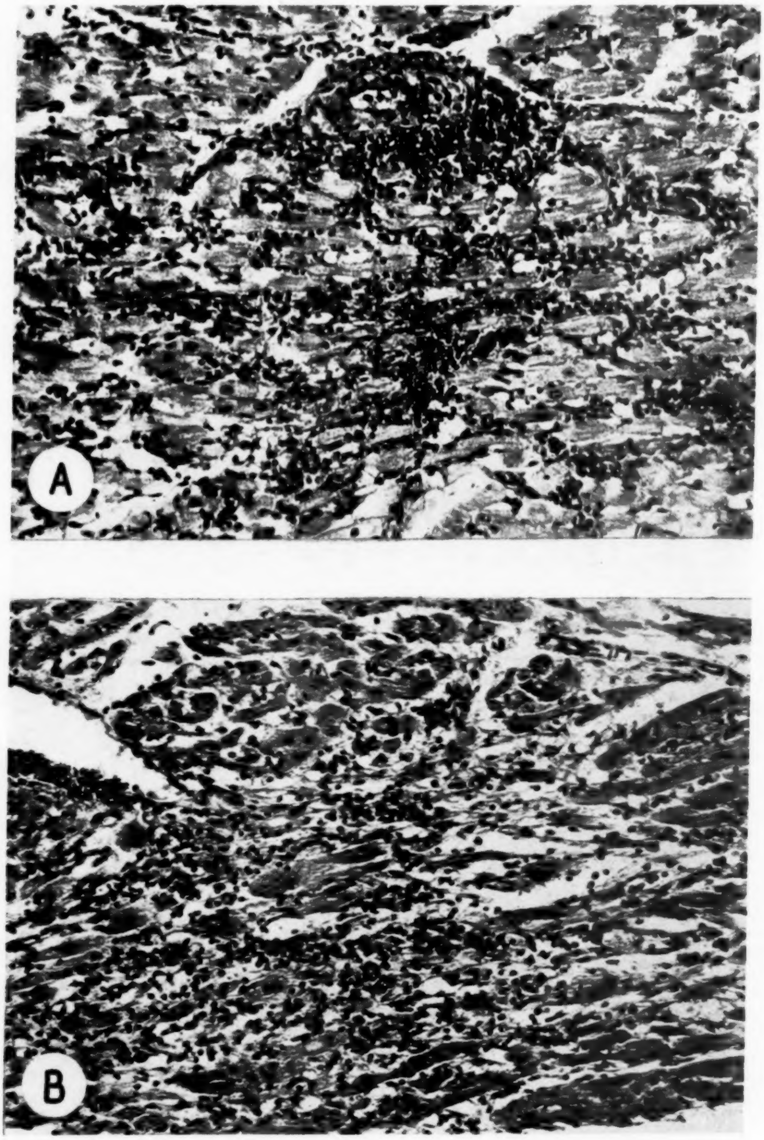

Fig. 2.—Sections of the myocardium of rabbit 7, killed 13 days after inoculation. *A.* Collection of leucocytes in the myocardium between and replacing muscle fibers. The exudate is concentrated at the margin of an arteriole. Hematoxylin and eosin, ×150. *B.* Diffuse leucocytic infiltration and myocardial necrosis. Hematoxylin and eosin, ×150.

Rabbits 9 to 15 were inoculated with virus which was presumably attenuated. Three of these animals failed to develop any clinically recognizable disease, and only one had myocardial lesions. In this latter rabbit, 9, and in one other, 10, the electrocardiograms were beyond the limits of normal variation.

Rabbits 16 to 25 were studied 14 to 24 days after the initial inoculation of virus which was known to be active. In none was there any

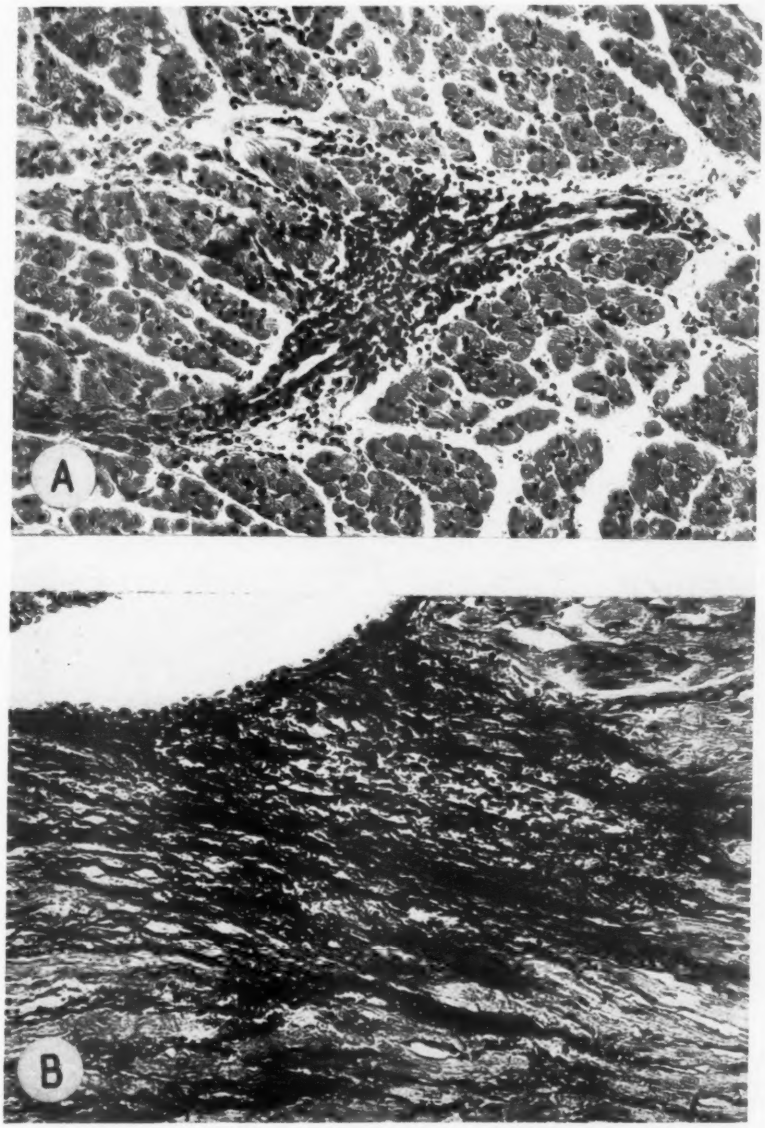

Fig. 3.—Sections of the myocardium of rabbit 7, killed 13 days after inoculation. *A*. Localized perivascular infiltration. Hematoxylin and eosin, ×150. *B*. Infiltration, necrosis, and fibrous tissue replacement in Purkinje's fibers of the right ventricle. Masson's trichrome stain, ×150.

clinical evidence of persisting infection. The majority of the hearts contained the small scars and focal collections of lymphocytes that are characteristic of a previous myocarditis, but in one, 25, the myocardial fibrosis and lymphocytic infiltration were extreme. This rabbit, 25, was the only one of the entire group in which the electrocardiogram was abnormal. When the record was first obtained, 24 days after inoculation, it showed paroxysmal auricular tachycardia with partial heart block (P-R interval, 0.12 second). Two days later normal rhythm had returned.

As shown in Table II, infection with the fibroma virus failed to bring about significant alteration in the electrocardiogram, even in those animals whose hearts contained lesions which could be demonstrated anatomically to be extensive.

DISCUSSION

The outstanding observation which can be made from the results of these experiments is the definite association of electrocardiographic abnormality with anatomic alteration. In other words, a morphologic cause of abnormal function is again demonstrated. In these infections of the rabbit, at least, the concept of toxicity, i.e., of some hypothetically intrinsic pharmacologic action of disease on the heart, as the cause of the abnormality of the electrocardiogram becomes unsatisfactory and untenable. With one exception, a significant variation from the normal rabbit electrocardiogram never occurred in the absence of histologically demonstrable myocarditis. This one exception, however, is not disturbing because it is easily conceivable that a small but locally severe lesion might occur in some part of the cardiac conduction system and yet be missed in the comparatively gross anatomic examination. Rather, it is surprising that there were not more animals with minute but significantly placed lesions which escaped observation but, nevertheless, changed the pattern of the electrocardiogram.

The value of the electrocardiogram in this type of disease is well shown by the fact that in the series of twenty-five animals there were only three in which the anatomic lesion in the heart was more than slight on which the diagnosis could not have been made by the abnormality of the tracing. This number represents a positive diagnostic accuracy of 88 per cent, a figure which compares well with other indirect methods of clinical examination. If the one rabbit (10) in which an electrocardiographic abnormality was encountered in the absence of a demonstrable lesion is included, the total diagnostic accuracy remains at the high figure of 84 per cent.

It is at first glance surprising that the animals inoculated with the inflammatory fibroma virus failed to develop any demonstrable irregularity in cardiac function. Reference to Table II, however, shows that even in those rabbits which were studied during the acute stage of the disease, when fever and orchitis existed, the myocarditis was marked in only two instances. With this virus in the present series of experiments, the lesion in the heart was more often an interstitial

proliferation of fibrous tissue, with little of the acute, inflammatory, exudative, and necrotizing reaction. The former type of reaction spares the structure of the muscle fibers, especially the conducting mechanism, so that no electrocardiographic abnormality may be expected. If this explanation is true, and since these animals were studied during the acute febrile period of their disease, the theory of toxicity as the cause of cardiac dysfunction again breaks down.

SUMMARY

Electrocardiographic studies were made on 25 rabbits which had been inoculated intratesticularly with virus III. During the acute stage of the resulting disease, the majority of these animals developed a histologically demonstrable myocarditis, and, after recovery from the infection, small scars were found in the myocardiums of many. Definite abnormalities in cardiac function, including complete auriculoventricular heart block, were demonstrated in the electrocardiogram during the period in which the acute myocarditis existed. The electrocardiogram failed to show the presence of a noteworthy myocarditis in only 3 animals, and in only one instance was it impossible to demonstrate myocarditis when the tracing was significantly altered. The electrocardiographic diagnosis was thus accurate in 84 per cent of the cases. This association of the abnormal electrocardiogram with the structural lesion in the heart leads to the conclusion that, in this disease of the rabbit, disturbed function is caused by actual lesions, and not by the toxicity of the disease.

Twenty-one rabbits which were inoculated intratesticularly with Andrewes' inflammatory strain of the Shope fibroma virus were studied similarly. Although in the hearts of a few of these animals interstitial myocardial fibrosis occurred, the muscle cells escaped for the most part, and in no animal was any abnormality in the electrocardiogram demonstrated.

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Clinical Reports

REPORT OF A CASE OF COR BILOCULARE WITH PERSISTENT TRUNCUS ARTERIOSUS

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COR biloculare with persistent truncus arteriosus was first described by Preisz,[1] in 1890. However, it was first fully described and studied by Abbott;[2] and in her series of 1000 cases of congenital cardiac disease it occurred nine times. The average duration of life in this series was three and three-fourths years. The patient who lived the longest attained the age of thirty-six, and was reported by Carr, Goodale, and Rockwell,[3] in 1935. The latter case of cor biloculare with persistent truncus arteriosus was similar in several respects to the present one and occurred in a male who, during his entire life, had a low cardiac reserve and was not cyanotic until a single period of strenuous exertion. Cyanosis then developed and gradually increased, and he died with congestive failure. The heart in this case was hypertrophied, and there was a single, large arterial channel arising from the right ventricle which was guarded by a semilunar valve with two cusps. The pulmonary arteries were exceptionally large and arose just above the valve. Directly beneath the arterial ring and valve there was a large interventricular septal defect.

Benjamin, Landt, and Zeek[4] reported a case of what was functionally a biloculate heart with a single arterial channel. Their patient, however, had an atretic right ventricle and pulmonary artery which, they believed, did not function. However, their specimen was incomplete in that the ductus arteriosus was not available for examination.

During the fourth week of intrauterine life a small ridge develops on the anterolateral surface of the common ventricle. At the same time a similar ridge develops in the truncus arteriosus, with four bulges at the base of this vessel. The bulbar septum divides one of these bulges, so that there are three to each trunk which become aortic and pulmonary valves. The ventricular septum and bulbar septum then fuse.

The present case is presented not only because of the rarity of this anomaly, but because of the apparently unusual fact that cyanosis occurred only shortly before death. The single arterial channel in this case had three well-developed semilunar cusps, and, according to some of the earlier authors, this would not be a true case of cor biloculare with persistent truncus arteriosus. However, according to Abbott,

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several well-authenticated cases with three cusps or even less have been reported.

CLINICAL RÉSUMÉ

The patient was a three-day-old white male, born in the San Francisco County Hospital. He was delivered by internal podalic version and extraction, and at the time of birth weighed 6 pounds, 3½ ounces. The infant breathed spontaneously; the color was described as good, and it was not cyanotic. No abnormalities were noted at the time of delivery. On the second day after delivery, the baby was transferred to the Isolation Department because of a small impetiginous lesion on the upper lip. Physical examination at that time by the pediatric resident revealed a small, newborn infant who was crying lustily and appeared quite healthy.

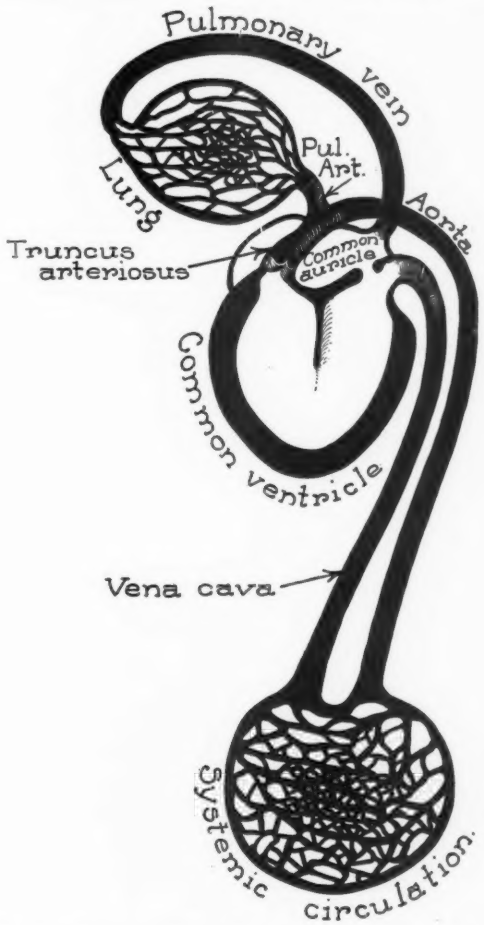

Fig. 1.—Diagram of greater and lesser circulation.

The baby had a definite subicteric tinge. The lungs were normal to percussion and auscultation. The heart was regular, and the sounds were of good quality. No murmurs were heard. The liver was palpable at the level of the umbilicus below the right costal margin. Later, on the second day after delivery, the extremities were noted to be slightly cyanotic, and, on the morning of the third day, the infant became extremely cyanotic, breathed with great rapidity and difficulty, and died suddenly.

AUTOPSY OBSERVATIONS

The autopsy was performed at the Coroner's Office of the City and County of San Francisco by the author. The body was that of a small male infant which weighed slightly less than six pounds and showed no external abnormalities. The lungs were only partially aerated, with numerous areas of collapse and edema.

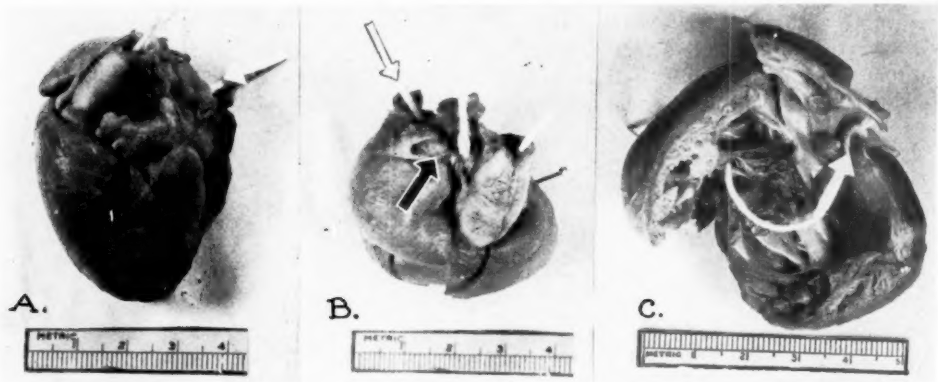

Fig. 2.—*A.* Anterior view of heart, black arrow indicating incompletely developed, nonfunctioning left auricle. White arrow and white line indicate direction of systemic blood flow.

***B.* Superior view, showing enlarged common auricle with truncus arteriosus and pulmonary artery. White arrow indicates direction of blood flow; black arrow indicates pulmonary veins.**

***C.* The heart opened up, showing the direction of blood flow and the semilunar valves at the base of the truncus arteriosus.**

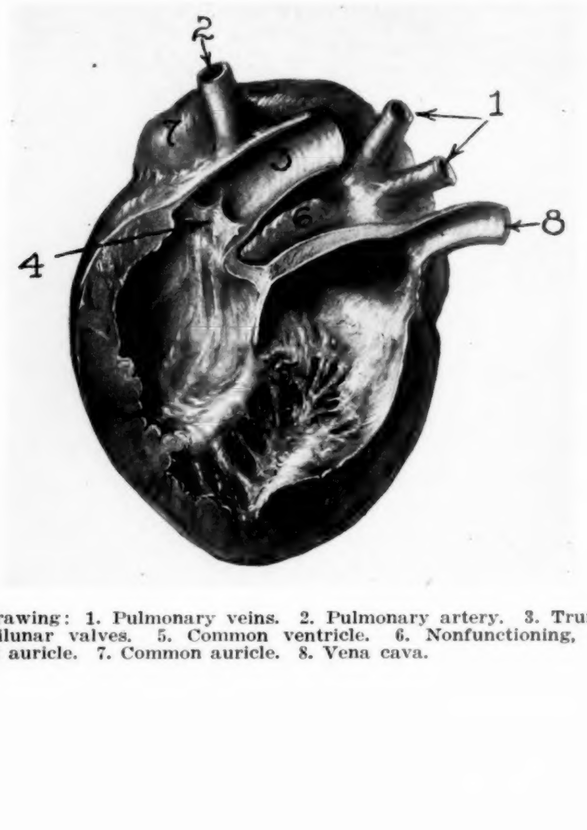

Fig. 3.—Drawing: 1. Pulmonary veins. 2. Pulmonary artery. 3. Truncus arteriosus. 4. Semilunar valves. 5. Common ventricle. 6. Nonfunctioning, incompletely developed left auricle. 7. Common auricle. 8. Vena cava.

The pulmonary arterial vessels were heavily congested. The heart was found to be enveloped in a normal pericardium and was not enlarged. It measured 3.5 × 3.0 × 5.0 cm. There were a single, large ventricular chamber and a single auricle. The vena cava emptied into the base of the auricle posteriorly on the right side. Slightly higher up, two small pulmonary veins also drained into the auricle. The functioning auricle lay on the right side, was smooth, and projected around the right side of the base of the heart like a large finger. A smaller appendage, with no lumen, was found projecting around the left side of the base of the heart. Near the opening of the functioning right ventricle a single, veil-like structure was attached to the ventricular wall by a poorly developed chorda tendineae. This resembled an incompletely developed atrioventricular valve or an incompletely developed membranous septum. Projecting from the right side of the common ventricle was a single, larger arterial channel, at the base of which was a semilunar valve composed of three well-developed cusps. Well above this valve was a single vessel which again divided and entered the pulmonary parenchyma on either side. The main vessel then continued on as the arch of the aorta, with its branches. The remaining portions of the aorta in the thorax and abdomen were not remarkable. The venous return from the lungs, as previously mentioned, was through two small veins which entered near the vena cava at the base of the functioning right auricle, or common auricle.

The remainder of the autopsy was not remarkable except for slight enlargement and congestion of the liver and spleen.

SUMMARY

A case of cor biloculare with persistent truncus arteriosus in a three-day-old infant, with the unusual feature that cyanosis occurred only shortly before death, is presented.

The blood flow through the lesser circulation was markedly increased at the time of birth, so that the systemic blood was well aerated or oxygenated, at least to the subcyanotic level; death was caused by diversion of some of the blood from the lesser to the greater circulation, thereby lessening the total output of oxygenated blood.

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ISOLATED DEXTROCARDIA, WITH DIODRAST STUDIES

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INTRODUCTION

EVERYONE is familiar with the mirror-image dextrocardia which almost invariably is associated with transposition of all the viscera. The rare cases of isolated dextrocardia are subject to associated cardiovascular anomalies and require individual study. In the case herein reported, visualization of the cardiac chambers by the diodrast method of Robb and Steinberg[15] was of great aid in understanding the pathologic anatomy. So far as we have been able to learn, this is the first study of its kind.

CASE REPORT

History.—B. I., a 55-year-old Italian housewife, was first admitted to Grasslands Hospital June 10, 1940. Beginning at the age of 35, or earlier, she had had attacks of "palpitation." These were usually accompanied by dyspnea and cyanosis, sometimes by vomiting and teichopsia, and once by hemoptysis. Dr. J. A. Costa, in referring her to the hospital, mentioned attacks of paroxysmal tachycardia which occasionally lasted several days and resulted in pulmonary edema, requiring oxygen therapy and full digitalization. Between attacks, which were diminished in frequency by the administration of one cat unit of digitalis daily, she felt perfectly well. In the week before admission she suffered two mild nocturnal attacks.

The family history and past history were essentially negative. Seven pregnancies were apparently well tolerated.

Physical Examination.—The patient was 59½ inches in height and weighed 125 pounds. She was lying comfortably in bed, without dyspnea or cyanosis. The point of maximum intensity of the heartbeat was felt in the right fifth intercostal space. The right border of the heart was percussed 11 cm. to the right of the midsternal line in the fifth intercostal space and 6 cm. in the third intercostal space. The left border was percussed 2 cm. to the left of the midsternal line in the fourth left intercostal space. The heart sounds were loud; the second sound at the base was louder to the right than to the left of the sternum. A loud systolic murmur and a faint, high-pitched, blowing diastolic murmur were present and were heard best in the right third intercostal space. The systolic murmur was widely transmitted over the entire precordium. No thrill was palpable. The blood pressure was 125/80 in both arms and 140/80 in the legs. The pulsation of the abdominal aorta was felt to the left of the vertebral column. The edge of the spleen was felt just under the left costal margin, and the liver descended, on inspiration, 4 cm. below the right costal margin.

Laboratory Examinations.—The Kline exclusion test was negative. The blood cell counts, the urine, the blood sugar, and the nonprotein nitrogen were normal. Between attacks the circulation times were: ether, 8 seconds, sodium cyanide, 13 seconds; paraldehyde, 9 seconds, and calcium gluconate, 12 seconds; the venous pressure was 10 cm. of water.

From the Medical Service of Dr. M. deTouart, Grasslands Hospital, Valhalla, N. Y.
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Roentgenographic Examinations.—The teleoroentgenograms of the chest showed that the heart was enlarged, and that it was in the right thoracic cavity, with considerable bulging of the right supraventricular shadow. The aortic knob was on the left. Fluoroscopic examination revealed increased pulsations of the right lower (ventricular) and supraventricular shadows. The aortic arch passed over the left main bronchus and descended on the left side of the spine. The aortic pulsations appeared to be normal. There was no "hilar dance."

An esophagram showed the usual left aortic arch impression upon the esophagus. The stomach was on the left, in the position in which it is found in normal persons (Fig. 1).

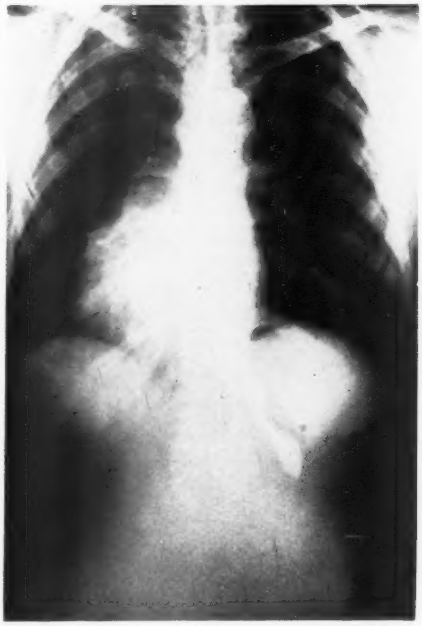

Fig. 1.

Fig. 2.

Fig. 1.—The heart occupies the right thoracic cavity. There is the usual left aortic arch impression upon the esophagus, and the stomach is on the left.

Fig. 2.—Roentgenogram taken two and one-half seconds after the injection of 50 c.c. of 70 per cent diodrast reveals a left-sided superior vena cava coursing downward and then to the right above the diaphragm to empty into the right auricle. The venous auricle and ventricle are seen on the right. The outflow tract of the venous ventricle forms a prominent conus on the right.

Roentgenograms were taken after the intravenous injection of 50 c.c. of 70 per cent diodrast, with the aid of Dr. Robb, according to the technique of Robb and Steinberg.[15] They showed that the venous auricle and ventricle were on the right side, with a left-sided superior vena cava coursing downward and then to the right above the diaphragm to empty into the right auricle (Fig. 2). The outflow tract of the right ventricle formed a prominent pulmonary conus. The left side of the posteroanterior roentgenogram (taken 10 seconds after the injection) was found to consist of the left ventricle and aorta (Fig. 3).

Electrocardiograms.—The first electrocardiogram (taken before admission) showed depressed S-T segments and diphasic T waves in all leads, with regular sinus rhythm and occasional premature ventricular contractions. A digitalis effect was evident. The electrocardiogram reproduced herewith (Fig. 4) is typical of those between attacks, when there was no digitalis or quinidine effect. It shows slurring

of the QRS in all leads, slightly depressed S-T segments in Leads I and II, a slightly elevated S-T segment in Lead IV F, an inverted T wave in Lead I and a QRS of 0.10 seconds. The next tracing (Fig. 5) reveals paroxysmal supraventricular tachycardia, with abrupt cessation on carotid pressure.

Fig. 3.—Roentgenogram taken ten seconds after the injection of 50 c.c. of 70 per cent diodrast shows the arterial ventricle and aorta forming the left side of the heart. The right side of the diaphragm is slightly lower than the left.

Course.—A mild attack of paroxysmal tachycardia was easily stopped by carotid pressure. An attack in July, 1940, was similarly controlled. The patient was readmitted July 20, 1940. She was dyspneic because of a five-day-old attack which had continued despite quinidine and vagal stimulation. It was again stopped by carotid pressure (Fig. 5). She was given 3 grains of quinidine four times a day, and 1/30 grain of strychnine three times a day after a second attack. On September 13, 1940, one week after stopping the above drugs, the patient was readmitted in another attack of paroxysmal tachycardia. She was dyspneic, orthopneic, and cyanotic, and had hypotension and generalized moist râles. The usual treatment for pulmonary edema was administered. Quinidine was given by mouth in a dose of three grains every three hours. The attack stopped after thirty grains had been administered. Previous to that, vagal stimulation, emetics, acetyl-beta-methylcholine, and quinidine intravenously had been ineffectual. Quinidine and strychnine were then continued in maintenance doses, and these kept her free from attacks for six months.

COMMENT

The following terms should be clarified. According to Lichtman,[7] "Dextrocardia" includes ". . . cases in which the heart, in its own de-

velopment independent of disease and anomaly in surrounding structures, assumes a position in the right side of the thorax with the apex pointing to the right." "Dextroversio cordis" includes ". . . cases in which the displacement of the heart is dependent on a congenital or acquired extrinsic cause." By "isolated dextrocardia" is meant "heterotaxia of the heart alone with normal position of all other viscera."

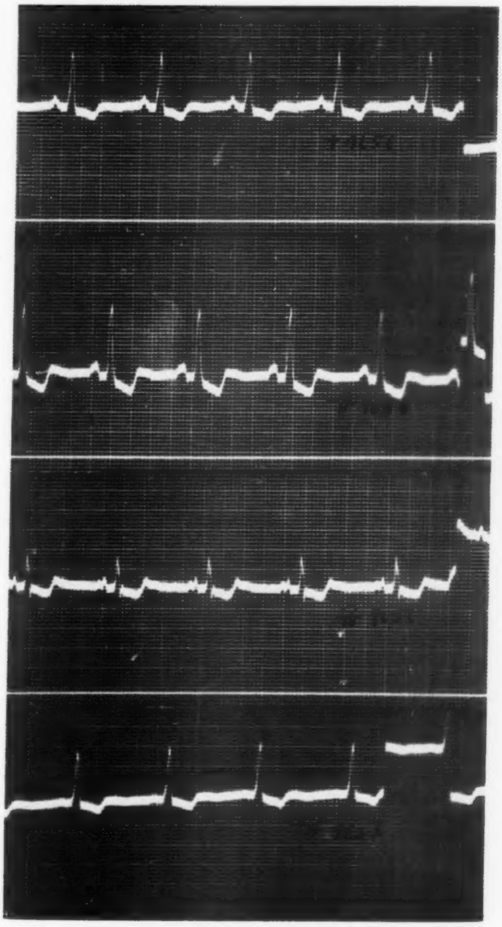

Fig. 4.—Electrocardiogram taken between attacks of paroxysmal tachycardia, when there was no digitalis or quinidine effect. Lead I shows the upright P and QRS, with the inverted T, which is fairly typical of isolated dextrocardia without "mirror-image."

Less than 200 cases of isolated dextrocardia have been reported. The case presented here is an example of the usual type of isolated dextrocardia, that is, without "mirror-image" inversion of the heart chambers. "Mirror-image" inversion always exists in situs inversus totalis, but rarely with isolated dextrocardia. In contradistinction to situs inversus totalis and isolated "mirror-image" dextrocardia, cases of isolated dextrocardia similar to the one herein reported are subject to other

cardiovascular anomalies. Lichtman[7] lists only three authentic cases of isolated dextrocardia without other cardiovascular anomalies. Although the life expectancy of patients with "isolated" dextrocardia (Roesler) is fourteen years, those who survive to the age of twenty may have a life expectancy of forty-four years. Symptoms and signs of congenital heart disease are usually evident in infancy in these cases, and death frequently occurs within the first year. Our patient is thus very unusual, if not unique, in having survived to the age of fifty-five. Certainly her seven pregnancies are rather remarkable. It is also noteworthy that none of her children has a demonstrable cardiac defect.

In a case reported in 1915, by Moffatt and Neuhof,[11] of isolated dextrocardia with many congenital cardiac anomalies and death at the age of three and one-half years, there were short runs of paroxysmal auricular tachycardia.

Few other arrhythmias associated with dextrocardia are reported in the literature. In Lichtman's second case of isolated dextrocardia[7] and Lloyd's[8] case of situs inversus totalis auricular fibrillation was present. In other cases, associated with acquired mitral stenosis, such as Krestin's,[5] there was the same arrhythmia. Abnormalities of the conduction mechanism have occurred rarely.[5, 10, 13] The arrhythmias in these cases have usually accompanied multiple cardiac defects, with enlargement of the heart and myocardial damage, as in our case.

The diodrast studies in our case clearly demonstrated the relationship of the heart chambers and the left-sided aortic arch (both of which are usual in isolated dextrocardia).[10, 16] Proof in the past has not been possible without post-mortem examination. From the diodrast and fluoroscopic studies we may conclude that the aorta was to the left of, and probably anterior to, the pulmonary artery, i.e., that these were transposed. In the terminology of Spitzer, 90° detorsion had taken place. The anomalous course and termination of the superior vena cava (we have not disproved the presence of a right-sided one as well) were also interestingly shown (Fig. 2).

It should be noted that the right side of the diaphragm was lower than the left, despite the presence of the liver on the right side. This is consistent with the theory[16] that the height of the diaphragm is influenced by the position of the heart rather than by that of the liver.

The electrocardiogram (Fig. 4) was characteristic of isolated dextrocardia, i.e., the complexes are upright in all leads except T in Lead I. Negative T waves in Lead I and sometimes in Lead II, as well as S-T segment deviations, may be found. There is no proof that the prognosis is made worse thereby, although the point is debatable.[16] This electrocardiogram is easily distinguished from that of mirror-image dextrocardia. The proof of the supraventricular origin of the tachycardia lay in the response to carotid pressure (Fig. 5) and the similarity of the QRS complexes during and after the attack. "Auricular leads" (not shown) proved the auricular origin of at least one attack.

Certain other changes in the electrocardiogram, particularly the widening and slurring of the QRS waves, point to diffuse myocardial damage. The presence of coronary insufficiency and myocardial fibrosis, in addition to whatever congenital lesions she had, is likely because of the age of the patient and the frequency of the paroxysms of tachycardia which resulted in congestive failure.

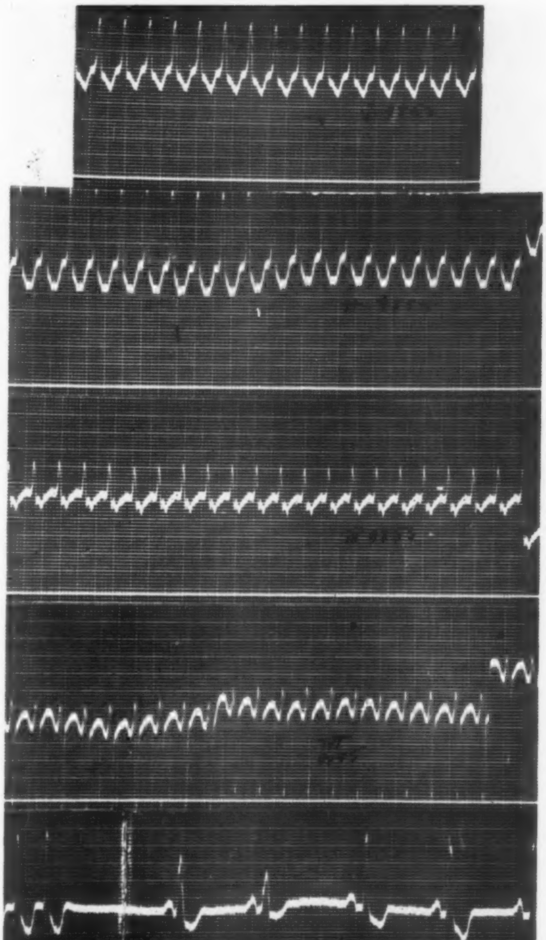

Fig. 5.—Electrocardiogram showing paroxysmal supraventricular tachycardia, with abrupt cessation on carotid pressure.

Finally, the nature of the lesion associated with the dextrocardia in this patient can only be guessed at. The murmurs were probably the result of either a pulmonary or an aortic lesion, and, since pulmonary stenosis or atresia is very common,[7] we may safely guess that such an anomaly was present here.

SUMMARY

1. A case of congenital isolated dextrocardia, without "mirror-image" inversion of the chambers, but with signs of congenital heart disease and attacks of paroxysmal tachycardia is presented.

2. The expected noninversion of the heart chambers was supported by diodrast and electrocardiographic studies. The "apex" of the heart was shown to be formed by the right (venous) ventricle. The left-sided aortic arch and superior vena cava were also demonstrated by diodrast visualization.

3. The rarity of the long survival of the patient and of the attacks of paroxysmal tachycardia is noted.

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The monograph of Roesler[16] contains about 350 references. The best review in English is that of S. S. Lichtman.[7]

PERSISTENT COMMON ATRIOVENTRICULAR OSTIUM

Report of a Case

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THIS congenital malformation of the heart is rare and is frequently associated with mongolism. Robinson,[1] in a recent review of the literature, found only thirty-nine cases, and many of them were only mentioned and not described. He added another case of his own. Of these forty cases, approximately one-half were in Mongolian idiots. Herein is presented another case of persistent ostium atrioventriculare commune in a child without mongolism or other major defects. This case is particularly interesting because there was an electrocardiographic and radiologic study.

CASE REPORT

The patient was a sixteen-month-old boy. He was born at full term, and breathed and cried spontaneously. The weight at birth was eight pounds. When three days old, the child was taken to the hospital because of dehydration, jaundice, and refusal to nurse at his mother's breast. At that time he was poorly developed, dyspneic, and cyanotic. On the right side of the head there was a hematoma the size of a hen's egg. Examination of the lungs was negative. The heart was of normal size, with no thrills and no murmurs. The rhythm was regular and the rate rapid. The child was given a transfusion, glucose, and a special feeding formula. He was discharged after eighteen days, much improved.

On the second admission, one month before death, the child appeared moderately dehydrated and extremely dyspneic. He had sat up at eight months but had not stood up nor crawled. He spoke his first word at eight months.

Physical Examination.—The patient was poorly nourished, poorly developed, moderately dehydrated, and markedly cyanotic. The temperature was 100° F., the respirations, 75 per minute, and the cardiac rate, 200 per minute. The chest had a pigeon breast appearance, with marked precordial bulging, mostly on the left side. The sternum was deformed and convex in shape. The apex impulse was diffuse and heaving. Numerous fine, crepitant râles were heard throughout both sides of the chest. The cardiac dullness was greatly increased; the left border of the heart was in the anterior axillary line. There were numerous murmurs over the precordium, and the rate was so rapid and the tones so loud that differentiation was impossible. The abdomen was scaphoid. The aortic pulsation was prominent. The edge of the liver was palpable and percussible three fingerbreaths below the costal margin.

Electrocardiogram.—The rate was 150 per minute and the rhythm regular. The P-R interval was 0.16 second. The QRS complexes were diphasic in all leads. The main deflections were downward in Lead I and upward in Lead III. The initial deflection was upward in Lead IVR and Lead IVF. P_1 and P_2 were prominent. P_3 was diphasic. The T waves were upright in all leads. The S-T segment take-off was 2 mm. low in Lead IVR and 2 mm. high in Lead IVF (Fig. 1). The electrocardiographic diagnosis was: (1) sinus tachycardia, (2) auricular hypertrophy, and (3) right axis deviation.

From the Department of Pathology, St. Louis University School of Medicine.
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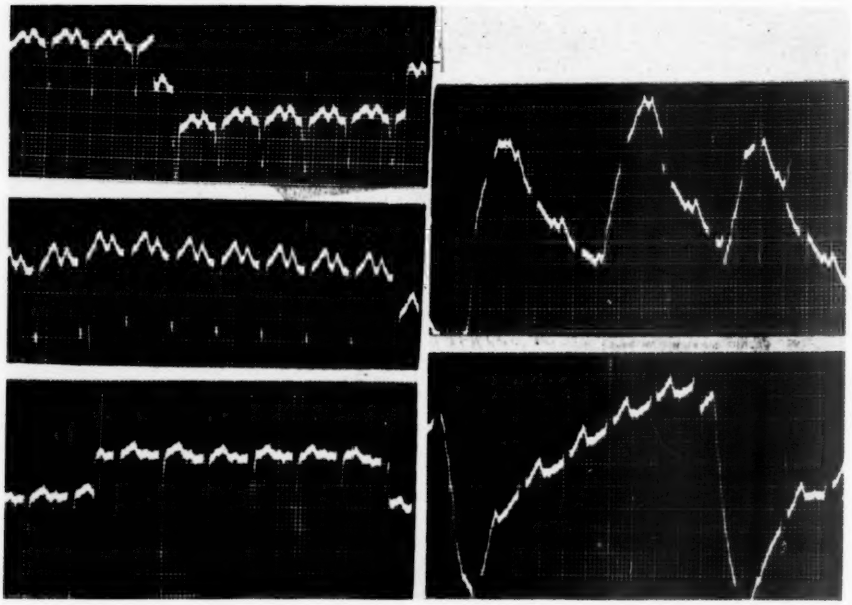

Fig. 1.—Electrocardiogram showing tachycardia, prominence of P_1 and P_2, and a diphasic P_3, right axis deviation.

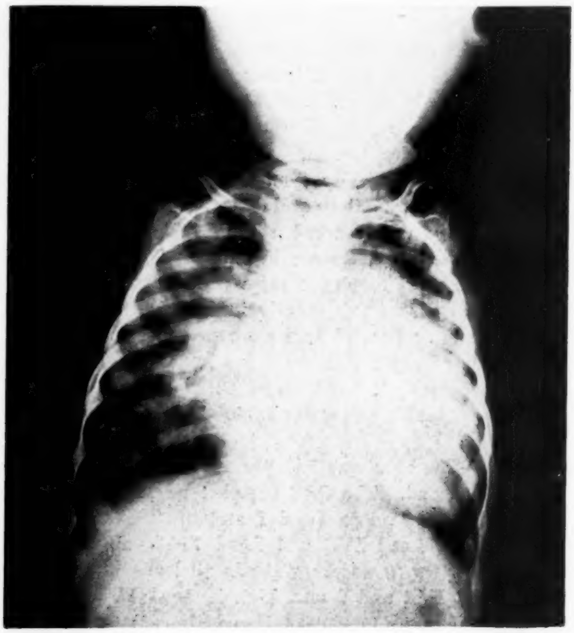

Fig. 2.—Roentgenogram showing marked enlargement of the cardiac outline and marked pulmonary congestion.

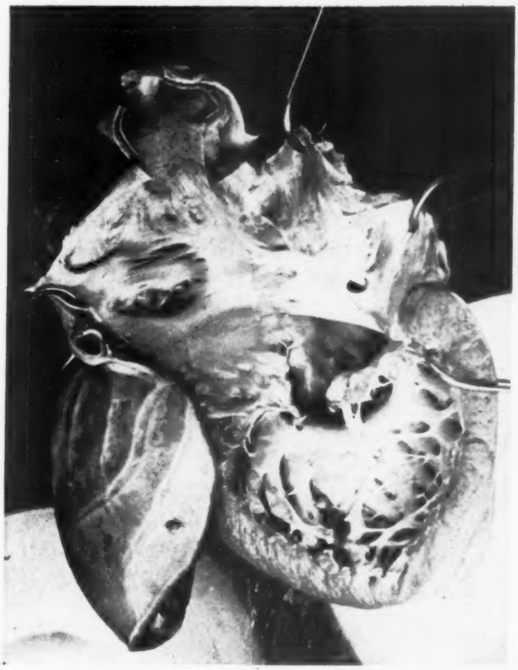

Fig. 3.—Left atrium and left ventricle. Common ostium with valve leaflets going through it.

Fig. 4.—Right atrium and right ventricle. Perforations in the interauricular septum.

Roentgenologic examination (Fig. 2) revealed an enormously enlarged cardiac shadow, with the left border extending to the axillary margin and the right border far to the right of the midline. There was also marked pulmonary congestion.

Laboratory Data.—The hemoglobin was 13 Gm., the erythrocyte count, 4,000,000, and the leucocyte count, 16,000. A differential leucocyte count showed 3 per cent metamyelocytes, 17 per cent nonsegmented polymorphonuclears, 52 per cent segmented polymorphonuclears, 2 per cent eosinophiles, 4 per cent monocytes, and 24 per cent lymphocytes.

Course in Hospital.—On the second day the patient's temperature was 102.5° F. He was cyanotic except when oxygen was being administered. On the fifth day his temperature was 102° F., and he had cyanosis and pronounced dyspnea. On the twentieth day his temperature was 102° F. He began to develop passive congestion and pulmonary edema, his temperature rose to 103.5° F., and his heart became irregular and rapid (155 per minute). He was very cyanotic and dyspneic, and died of congestive heart failure.

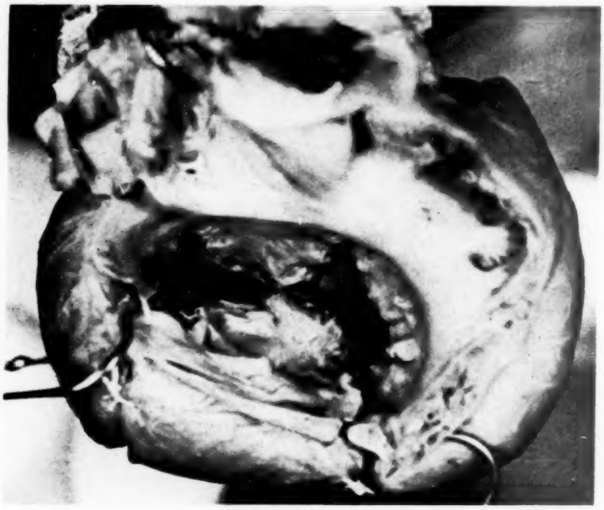

Fig. 5.—Common atrioventricular orifice with six valvular leaflets: two common leaflets (across midline), one leaflet in the left ventricle, and three in the right ventricle (two of these are rudimentary).

Autopsy.—The anatomic diagnoses were (1) persistent common atrioventricular ostium, (2) congestive heart failure, with hypertrophy and dilatation of the heart, (3) hydrothorax, (4) pulmonary congestion and edema, and (5) congestion of all viscera.

The heart weighed 119 grams. There was marked dilatation of the whole heart, but chiefly of the right side. The epicardium was thin and intact. The myocardium was markedly thickened, measuring 0.7 to 0.8 cm. in the right ventricle and 0.8 to 1.0 cm. in the left ventricle. The endocardium of the right ventricle was somewhat thickened, white, and opaque. In the left ventricle the endocardium was thin and intact. There was a large defect of the lower part of the auricular septum and the upper part of the ventricular septum (Figs. 3 and 4). This defect had a round shape and measured 2 cm. in diameter. Through the defect in the atrioventricular septum there were two large valve leaflets, one anteriorly and one posteriorly, going from one ventricle to the other. These two common leaflets had chordae tendineae attached to the upper, concave border of the interventricular septum. In the right ventricle, beside the two halves of the common cusps, there were a well-developed

leaflet and two small, rudimentary ones. In the left ventricle there was only one valve cusp in addition to the two left halves of the common leaflets (Fig. 5).

The foramen ovale was closed, but below the fossa ovalis, posteriorly, there were two small perforations of the auricular septum about 2 mm. in diameter. The aortic and pulmonary valves were essentially normal and measured 1.5 cm. in diameter.

According to Mall[2] and Gunn and Dieckmann,[3] this developmental anomaly is caused by an arrest of growth of the heart in early intrauterine life. This arrest of development has to do with the interauricular septum, the interventricular septum, and the endocardial cushions. This lack of development of the cardiac septa leaves a wide communication between the different chambers of the heart. During cardiac diastole, when the atrioventricular valves are open, the four chambers of the heart communicate with each other. During cardiac systole, when the A-V valves are closed, the two atria communicate with each other and the two ventricles with each other.

SUMMARY

A case of persistent ostium atrioventriculare commune is presented. Forty cases have been mentioned or described in the literature, and about half of these were associated with mongolism.

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AURICULAR STANDSTILL

Verne S. Caviness, M.D., Raleigh, N. C.

THE sinoauricular node, the pacemaker of the heart, was discovered by Keith and Flack, in 1907. It is at the end of the sulcus terminalis at the junction of the superior vena cava and the right auricle. It consists of nerve cells, nerve fibers, and heart muscle cells, imbedded in fibrous tissue. The nerve fibers are connected with the vagus nerves and the sympathetic trunks. The blood supply is rich and is received through a coronary artery branch. Sudden death has been reported from the occlusion by a syphilitic process of the mouth of this artery in the aorta.

MISSED BEATS

Disturbances in the sinoauricular node appear to be quite infrequent. When present, they are usually of short duration.[1] Sinoauricular block is the usual abnormality and is characterized by missed beats which should be differentiated from extrasystoles.

Sinoauricular block[2] produces a pause in the cardiac rhythm, and, because of the lack of the compensatory pause which follows extrasystoles, it is usually of less duration than two cardiac cycles. It may occur in healthy persons, e.g., athletes, after strenuous exertion, or after excitement. In children[2, 3, 5] it may follow severe infections, such as diptheria or rheumatic infections. Syphilis is an occasional cause. The most frequent cause is poisoning by digitalis. Quinidine[4] may be a factor, especially when given with large doses of digitalis. Nervous exhaustion appears to be a contributing factor. It is not affected by strychnine, bromides, or theobromine.[6] Nitrites and atropine tend to decrease the frequency of missed beats. Exertion appears to have a similar influence on some patients. Excessive smoking has been alleged by one observer to produce sinoauricular block.

Sinoauricular block is not to be confused with sinus bradycardia, in which the slow rate might suggest that alternate beats are being dropped. The gradual development of the bradycardia and the gradual recovery obviate the conclusion that there is a disturbance in rhythm.

AURICULAR STANDSTILL

Sinoauricular block in its most severe form is termed auricular standstill. This is a very rare condition. In 1939, Rosenbaum and Levine[3] found eight cases in the literature and added a like number from the Massachusetts General Hospital. They added four possible cases to each group. No additional cases appear to have been reported.

Auricular standstill can be diagnosed only by the electrocardiogram.

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There is no evidence of auricular activity, and the ventricles beat with a regular, independent rhythm. The mortality is very high, probably because of the degree of digitalis poisoning required to produce auricular standstill. It is not known whether there is a total blockage of transmission of impulses or whether impulses are not formed.

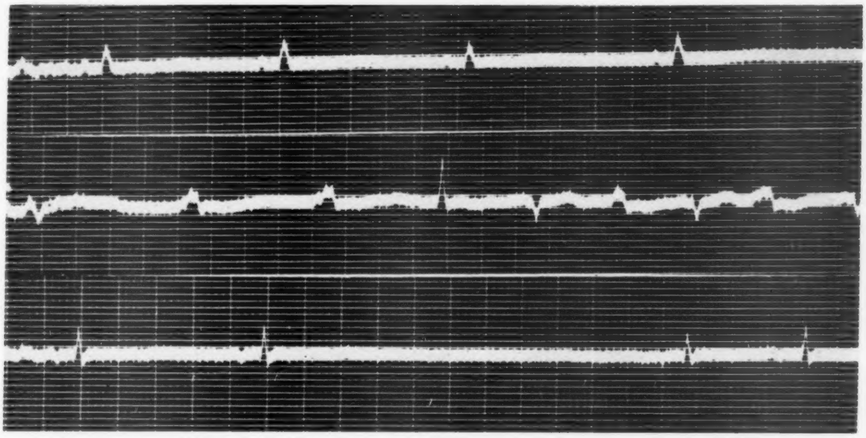

Fig. 1.—Mrs. L., May 4, 1941. Toxic digitalis effect: bradycardia, auricular and ventricular extrasystoles; Lead II shows only one normal beat and it appears to follow a P wave; Lead III shows a long interval, 2⅓ seconds, of auricular and ventricular inactivity.

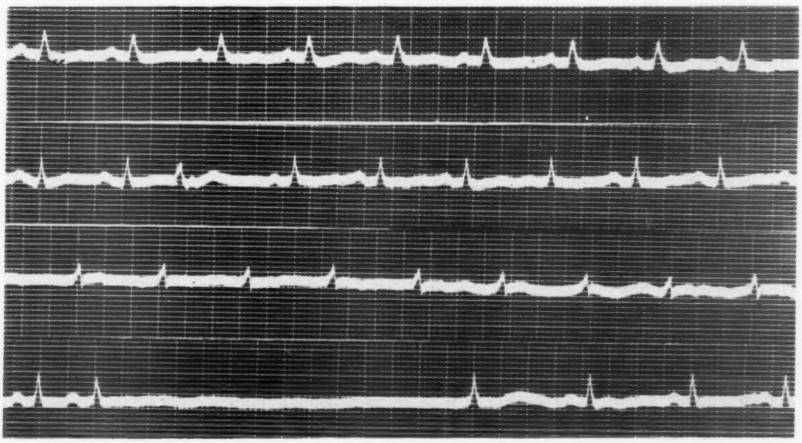

Fig. 2.—Mrs. L., May 8, 1941. Digitalis stopped and rhythm improved; P waves almost entirely absent in Lead III; Lead IV shows a period of 2⅘ seconds of auricular and ventricular inactivity.

It appears likely that the condition is much more frequent than would be indicated by statistics: it is probable that many unexplained sudden deaths during digitalis therapy are caused by auricular standstill. Various factors, including digitalis poisoning, might account for failure of the ventricles to develop an independent rhythm.

Rest is often the best form of therapy and should be used far more than appears at times to be possible. Digitalis is a good crutch for a damaged heart, but it is also a very dangerous and poisonous drug when

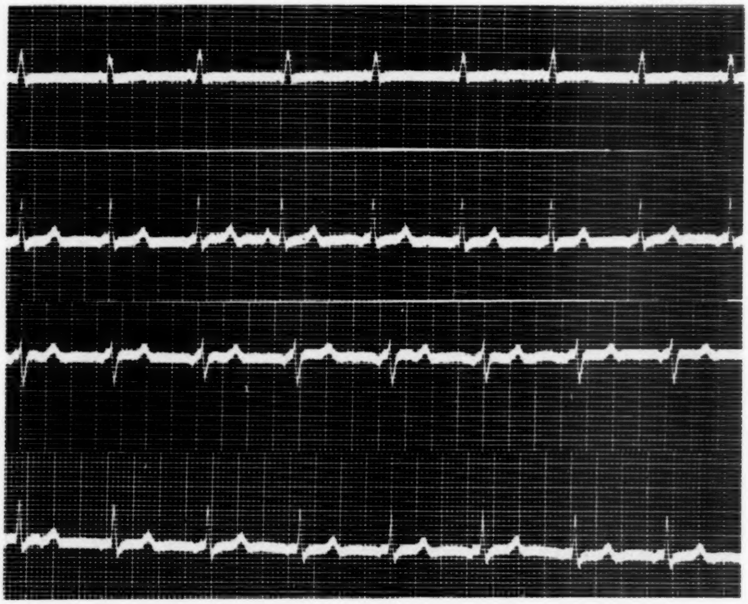

Fig. 3.—Mrs. L., June 9, 1941. No digitalis; conduction time shortened to half that of earlier tracings; rhythm regular.

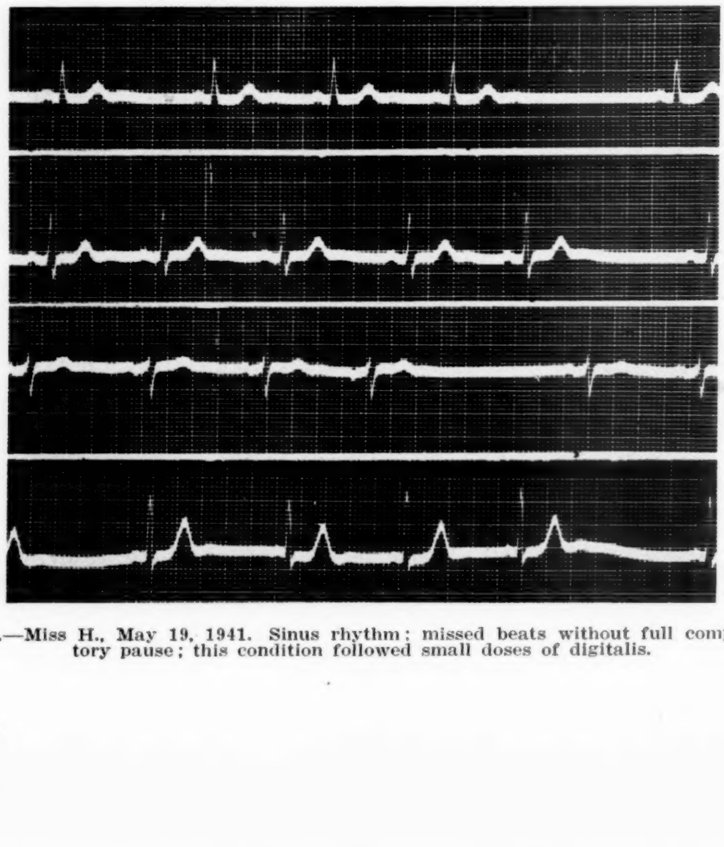

Fig. 4.—Miss H., May 19, 1941. Sinus rhythm; missed beats without full compensatory pause; this condition followed small doses of digitalis.

used in large doses. It is doubtful whether a large dose of digitalis is more effective than a small dose. When a small dose fails to improve the cardiac output, larger doses rarely, if ever, improve the results. Also, often it is impossible to slow the cardiac rate by digitalis; for various reasons, a rapid rate may be needed for an adequate circulation, and efforts to slow such a tachycardia by digitalis may be expected to end in disaster. Variability of individual susceptibility to the drug increases the danger from digitalis and necessitates greater care in its use.

Figs. 1, 2, and 3 are electrocardiograms of a patient who developed an irregular, rapid pulse after surgical drainage of her gall bladder. For three days she received, hypodermatically, sixteen ampoules of digifoline and ten ampoules of coramine. Part of the time she was given two ampoules of digifoline every three hours. The third tracing shows the result in her case of stopping digitalis. Death is the usual result.

Fig. 4 shows sinoauricular block with typical missed beats, not fully compensated, apparently caused by taking one cat unit of digitalis daily for five days. The digitalis was stopped, and, after several weeks, regular rhythm was gradually restored.

CONCLUSION

These two cases, one of auricular standstill and one of sinoauricular block, are quite interesting from the standpoint of rareness as well as etiology.

It is possible that auricular standstill may not be so rare as has been supposed. Adequate use of the electrocardiograph might show that this condition is quite common, not only as a terminal event, but also as a result of infections, digitalis, and strenuous exertion.

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Abstracts and Reviews

Selected Abstracts

Yanof, Z. A.: Blood Pyruvic Acid in Heart Disease. Arch. Int. Med. **69**: 1005, 1942.

There is a rise above normal of pyruvic acid in the blood of persons with heart failure. This elevation approximates the degree of failure.

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Herrmann, G., Decherd, G. M., and Calvin, D. B.: The Application of Blood Volume Studies to the Theory of the Mechanism of Diuresis. Tr. A. Am. Physicians **56**: 298, 1941.

Serial blood plasma volume studies following the intravenous injection of diuretics, aminophyllin, salyrgan, mercupurin, and digoxin have yielded further evidence as to the various mechanisms that initiate and accompany diuresis.

With the mercurials and the xanthines given intravenously there seems to be definitely primary renal effects and probably subsequent secondary extrarenal effects.

It is not possible by these present studies to localize absolutely the site of the renal or extrarenal action. Diuresis is not dependent upon the rise in blood plasma volume. It may continue with falling blood plasma volumes and drop off with rising blood plasma volumes. At any one time the blood plasma volume is the resultant of urine excretion through the kidney and movement of fluid from or to the tissue interstices.

The total blood volume shifts usually are not commensurate with the volumes of urine excreted.

AUTHORS.

Nahum, L. H., Hoff, H. E., and Kaufman, W.: The Nature of the S Complex of the Electrocardiogram. Am. J. Physiol. **136**: 726, 1942.

The downstroke of S_3 develops with the complete activation of the posterior surface of the left ventricle while a portion of the anterior surface of the right ventricle is not yet active.

The upstroke of S_3 occurs when the remainder of the anterior surface of the right ventricle becomes active and restores isopotentiality.

The same sequence of ventricular excitation explains the presence of an S_3 in the ventricular extrasystole.

S_1 probably arises from a similar sequence of excitation in the anterior left and posterior right ventricles.

AUTHORS.

Groedel, F. M., Kisch, B., and Reichert, P.: Changes in the Standard Electrocardiogram and the Chest Leads During the First Stages of Life. Cardiologia **6**: 1, 1942.

While in the adult with normal heart conditions two different chest electrocardiograms, the left and the right, always exist, the newborn seems to show immediately after birth, usually over the whole thorax, only one pattern, that of the

right chest electrocardiogram. This pattern changes in the left axilla line generally after a few hours, but not infrequently after days, into that of the left electrocardiogram. On the contrary the chest electrocardiogram led from the sternum does not change its character during the first life span, only the coefficient R-height to S-height alters, insofar as, during the first days of life, the coefficient resembles that found in older adults, while it changes later on to that found in children and younger adults.

AUTHORS.

Groedel, F. M., and Kisch, B.: Morgagni-Adams-Stokes Syndrome: What Does It Represent? Cardiologia **6:** 43, 1942.

The M.A.S. syndrome is a condition of attacks of unconsciousness, with or without the occurrence of convulsions and incontinence of urine and bowels, caused by an acute ischemia of the central nervous system. The causative factors of such attacks are always acute disturbances of the heart action leading to an insufficient blood supply to the cerebrum. We observe the syndrome occurring in two groups of heart disease, in cases suffering from heart block and in patients suffering from tachycardia or salvos of ventricular extrasystoles or attacks of ventricular fibrillation. Abortive cases are also very frequent. These patients likewise suffer from different types of short attacks of tachycardia, paroxysmal auricular fibrillation and attacks of extrasystoles, leading only to a lesser degree of cerebral ischemia and, therefore, the patients are complaining about only fainting-like spells. We never observed a case of M.A.S. syndrome due to sinus bradycardia, although such cases are referred to in the French literature.

AUTHORS.

Hermann, B., and Decherd, G. M., Jr.: Tachycardias: Diagnosis and Treatment. New Orleans M. & S. J. **94:** 417, 1942.

Sinus tachycardia is due to a variety of causes and sometimes will be slowed by vagus stimulation either through the carotid sinus, or by drugs such as pilocarpine or prostigmine or neosynephrin. Digitalization is effective in cases with heart failure, indirectly by improving the circulatory efficiency, or directly by precipitating fibrillation and A.V. block.

Paroxysmal tachycardias are briefly discussed from the clinical and electrocardiographic points of view. Those from a supraventricular focus are managed by trying first the effects of reflex vagal stimulation. Acetyl-Beta-methylcholine or prostigmine methyl sulphate are sometimes successful. Quinidine has been used as have various digitalis preparations as digoxin, digilanids or lanatoside C or digitalis extracts, either by mouth or intravenously. Quinidine or potassium salts are used prophylactically. For the paroxysms from a ventricular focus, due usually to a myocardial infarction, quinidine is the only drug to be recommended.

Tachycardias due to circus mechanisms, auricular flutter and auricular fibrillation are described. Digitalization converts a flutter to a fibrillation, and cinchonization is usually then necessary to establish a sinus rhythm. Quinidine alone without preliminary digitalization is often efficacious in auricular fibrillation cases of short duration and it is justifiable to use quinidine in an attempt to establish the normal rhythm. Digitalis usually controls the ventricular rate when the auricles are fibrillating.

For details of diagnosis and dosage the original may be consulted.

AUTHORS.

Stein, W., and Uhr, J. S.: Congenital Heart Block: Report of a Case. Brit. Heart J. **4:** 7, 1942.

Because of its comparative rarity, another case of congenital heart block occurring in a white three-year-old female child is added to the literature. The ac-

cidental manner in which the anomaly was discovered after the youngster had been hospitalized and operated upon for a right acute mastoiditis is related.

The pathology of the abnormal embryological development of a patent interventricular septum and its association with congenital heart block is discussed.

AUTHORS.

Urbach, E., Loew, A., and Gottlieb, P. M.: Bronchial Asthma and Cardiopathy. Cardiologia **6:** 13, 1942.

Damage to the heart will often develop during the course of an asthma of long duration. This involves the myocardium, never the endocardium. For hemodynamic reasons, the right ventricle is affected first. But not infrequently, especially in older asthmatics, the left heart may become affected, the disorder being manifested clinically as angina. Attention has been drawn to the possible etiological relationship between bronchial asthma and coronary disease. Recognition of the cardiac involvement and understanding of its pathogenesis are of importance in therapy. The authors point out the value of electrocardiograms in every case of asthma. These should be taken not only in the free intervals, but also after effort, and if possible, during the attack of asthma. The theory is expressed that electrocardiographic changes occurring only during asthmatic attacks are caused by myocardial anoxia.

Emphasis is placed on the necessity of roentgenological examinations for the early determination of stasis in the lesser circulation as a sign of associated involvement of the heart. The point is stressed that remarkable results are achieved by the intravenous administration of strophanthin, aminophylline, and glucose in cases of asthma where involvement of the heart cannot be demonstrated by clinical and electrocardiographic methods.

AUTHORS.

Duchosal, P. W., and Henny, G.: Angina Pectoris and Hyperthyroidism. Cardiologia **5:** 372, 1941.

A 50-year-old woman had all signs of a hyperthyrosis, the appearance of which was noted in the menopause. Progressive emaciation, increased metabolic rate, and attacks of typical angina pectoris in rapid succession were experienced. Treatment with lugol brought immediate improvement and temporary disappearance of the angina pectoris. Strumectomy was performed, shortly after which the patient died. The electrocardiograms showed very great variability in the course of the hyperthyreotic periods. The characteristic change was an extreme but temporary increase of the S-T piece. This change appeared independently from the angina pectoris, usually, however, following exertion. It was also observed after the apnea and hyperpnea tests, however, spontaneously.

The anatomic examination showed the coronary arteries and their branches into the capillaries to be fully intact. The myocardium was the seat of a large number of degenerative centers of especial appearance. They reminded one of the toxic conditioned changes in the course of tuberculosis. The anatomical examination of the goiter showed two very small adenomas of Basedow infected tissues to be the only cause of this severe thyreotoxicosis.

An explanation of the angina pectoris, founded on the hypothesis of the factor P after Lewis, is given.

AUTHORS.

Raab, W.: Abnormal Suprarenal Discharges in Angina Pectoris and Their Control by X-ray Therapy. J. Clin. Endocrinol. **1:** 977, 1941.

Adrenocortical (AC) compounds, which consist of adrenalin combined with cortical sterols were quantitatively determined by a chemical method in the blood of individuals with and without angina pectoris.

In angina patients the blood AC level, although generally normal at rest, showed abnormally intense, sharp elevations after physical exercise. These elevations persisted for several minutes. The AC compounds which were discharged into the blood stream during physical exercise were particularly rich in adrenalin.

Therapeutic roentgen irradiation of the suprarenal glands, if successful, resulted in disappearance of the abrupt AC discharges on effort, coinciding with complete or almost complete disappearance of the subjective anginal symptoms for periods of several months.

The significance of these observations is discussed from the point of view of the theory that angina upon effort is caused by the specific anoxiating effect of sudden suprarenal discharges upon the heart muscle whose oxygen supply is inadequate, due to sclerosis of the coronary arteries and their inability to dilate adequately.

AUTHOR.

Poel, W.: Cardiometric Studies on Children. III. Report of a Case of Incomplete Heart Block Due to Vagal Effect. Arch. Int. Med. **69:** 1040, 1942.

A case of persistent functional heart block apparently due to vagal influence is presented. Three previously described cases of such disturbance are reviewed.

The frequency of occurrence of this phenomenon in normal adolescents is low. It was encountered only once in 2,400 electrocardiograms made on normal persons between the ages of 12 and 20.

Body position, body activity and respiration were found to have a definite effect on the duration of the PR interval in the case reported here. Respiration also affected the intensity and audibility of a third heart sound, or auricular sound.

Observations pertaining to the effect on the heart of experimental excitation of the vagus nerve are reviewed. A possible explanation of the origin of functional heart block is suggested in the light of these observations.

AUTHOR.

Hayes, R. M., and Gibson, S.: An Evaluation of Rheumatic Nodules in Children: A Clinical Study of 167 Cases. J. A. M. A. **119:** 554, 1942.

Of 167 children with rheumatic nodules, 86 were boys and 81 girls. The age incidence of patients with nodules closely paralleled the age incidence in the group with rheumatic infection in general. Nodules were found in many regions, the most frequent locations being the elbows, knees, scalp, knuckles, malleoli, and vertebral spines. Nodules on the extremities tended to be symmetrical in their distribution. The duration of nodules varied from a few days to several months. Other rheumatic phenomena were present in every case. Rheumatic heart disease was found in 163 cases. Fifty-two patients (31 per cent) died. The number of nodules in the individual case was not found to be important in determining the prognosis.

AUTHORS.

Schwartz, S. P., and Marcus, H.: The Electrocardiogram in Pulmonary Tuberculosis. I. The Clinical Significance of Concordant Inverted Initial Ventricular Deflections in Patients With Chronic Pulmonary Tuberculosis. Am. Rev. Tuberc. **46:** 35, 1942.

A study was made of the clinical significance of electrocardiograms showing a concordant type of inverted initial ventricular deflections in the standard leads in 7 patients with chronic pulmonary tuberculosis.

In 2 patients, the appearance of this pattern was associated with signs of congestive heart failure and recognizable enlargement of the heart as judged from

comparison of roentgenograms and fluoroscopic examination. In 5 patients the appearance of this pattern was found to be associated with symptoms of severe dyspnea and cyanosis but with a relatively small heart in the roentgenograms.

In 3 patients, in addition to the downwardly directed QRS complexes there was enlargement of the P-waves in Leads II and III and abnormal variation in the RS-T segment in Leads II, III, and IV.

In 6 of the patients who came to necropsy this electrocardiographic pattern was found to be associated with either hypertrophy alone, hypertrophy and dilatation, or dilatation without hypertrophy of the right ventricle and occasionally the right auricle.

These correlated observations suggest that in patients with chronic pulmonary tuberculosis the appearance of downwardly directed deflections of the QRS complex are an index of changes in the muscle mass or the size of the right ventricle causing a rotation of the heart around its longitudinal axis.

Since respiratory distress and increasing cyanosis in patients with chronic pulmonary tuberculosis may be due either to the progression of the pulmonary lesion or to right heart failure in the absence of signs of congestion, this electrocardiographic pattern may be the only clue that the symptoms are the result of cardiac embarrassment.

This pattern being persistent and irreversible, its presence is of ominous prognostic significance. None of the patients with chronic pulmonary tuberculosis who showed it lived longer than one year.

AUTHORS.

Grollman, A., and Williams, J. R., Jr.: Experimental Hypertension in the Rat. Am. J. M. Sc. **204:** 73, 1942.

A variety of procedures is outlined by which it is possible to induce chronic hypertension in the rat. The most practical of these procedures consists in applying silk to the kidneys. This is accompanied by relatively low operative mortality and usually results in a permanent elevation of pressure to hypertensive levels. The blood pressure responses to various other operative procedures on the kidneys are described.

AUTHORS.

Chasis, H., Goldring, W., and Smith, H. W.: Blood Pressure Reduction Associated With Pyrogenic Reaction in Hypertensive Subjects. J. Clin. Investigation **21:** 369, 1942.

Blood pressure can be reduced significantly in hypertensive subjects by the intravenous administration of pyrogenic material (pyrogenic inulin, triple typhoid vaccine, tyrosinase), and it can be maintained at reduced levels by the repeated injections of this material. This hypotensive effect can be obtained without a rise in body temperature by premedication with amidopyrine.

The mechanism responsible for the persistent blood pressure reduction is unknown, but, from the more immediate effects of pyrogen, it appears to be attributable in part to an adverse or asthenic action on the cardiovascular system, rather than a correction of the fundamental disturbance underlying the hypertensive process.

One instance of a marked reduction in blood pressure in a hypertensive subject during a postcystoscopic febrile reaction is illustrated. Such reactions are reported to be attributable to a transient B. coli bacteremia, and the reduction of blood pressure here, and in other acute infections, may be associated with the pyrogenic reaction associated with the infection.

Whenever the blood pressure of a hypertensive subject is reduced by the parenteral administration of a foreign organic material, this pyrogenic type of

response should be excluded before a specific hypotensive property is attributed to the agent used. And any pyrogenic material should be administered cautiously, since it may induce an alarming degree of peripheral circulatory failure, as illustrated by one of our subjects.

AUTHORS.

Kempf, G. F., and Page, I. H.: Production of Experimental Hypertension and the Indirect Determination of Systolic Arterial Pressure in Rats. J. Lab. & Clin. Med. **27**: 1192, 1942.

Silk perinephritis and constriction of the renal artery by a silk thread both elicit arterial hypertension in rats of a degree sufficient for assay of renal antipressor extracts. The preparation of hypertensive rats by these methods is described.

The method of Williams, Harrison, and Grollman for measurement of systolic blood pressure has been modified to increase its effectiveness.

AUTHORS.

Kaiser, I. H.: The Specificity of Periarterial Fibrosis of the Spleen in Disseminated Lupus Erythematosus. Bull. Johns Hopkins Hosp. **71**: 31, 1942.

The splenic pathology in 18 cases of disseminated lupus erythematosus is summarized. Perisplenitis and periarterial fibrosis were the commonly observed lesions. Periarterial fibrosis was found in 15 of the 18 cases in this series.

The perisplenitis presents no characteristics by which it may be differentiated from that commonly seen in other conditions.

Periarterial fibrosis is defined herein as the occurrence of at least three separated layers of the normally densely packed periarterial collagen of penicillary and follicular arteries, in such a manner as to give the typical ringed appearance. The collagen is frequently hyaline and granular eosinophilic material may be found continuous with it. The process apparently is an alteration of collagen independent of necrosis or inflammation. No early or intermediate stages have been observed.

In the control series of 1679 splenic sections periarterial fibrosis occurred in 53 cases, an incidence of 3.2 per cent. No evidence of the occurrence of disseminated lupus erythematosus could be found in any of these cases.

Periarterial fibrosis occurred in 4 cases of essential thrombocytopenic purpura out of 13 examined, an incidence of 31 per cent. This is the only group besides the cases of disseminated lupus erythematosus which significantly differed from the control series.

The splenic lesions of disseminated lupus erythematosus are not pathognomonic of that disease, although periarterial fibrosis occurs in a very high proportion of the cases. There are no known characteristics of the splenic periarterial fibrosis found in disseminated lupus erythematosus which will distinguish it from that found in other conditions. In view of its frequent occurrence in disseminated lupus erythematosus, however, the discovery of the lesion at autopsy should raise a suspicion of disseminated lupus erythematosus and provide impetus for further investigation. When found in association with the other familiar stigmata of disseminated lupus erythematosus periarterial fibrosis in the spleen provides corroborative evidence.

AUTHOR.

Hess, L.: On the Crista Terminalis. Cardiologia **5**: 388, 1941.

It is suggested that the Crista terminalis may play a peculiar and not unimportant role during the systole of the auricle.

AUTHOR.

Lake, M., Pratt, G. H., and Wright, I. S.: Arteriosclerosis and Varicose Veins: Occupational Activities and Other Factors. A Study of 536 Persons, Divided Into Age Groups, Who Had Been Sitting, Standing, Walking or Climbing Stairs for Ten Years or More at Their Work. J. A. M. A. **119:** 696, 1942.

Men had a higher incidence of arterial disease than did women of the same ages who had been employed at similar occupations an equal length of time. Among the younger men (age group 40 to 49 years), stair climbing apparently produced a significantly higher incidence of arteriosclerosis than did standing, sitting, or walking. No significant difference could be established among the last three classifications. Over the age of 50 there were no significant differences in the incidence of arterial disease in any of these classifications.

The use of alcohol and tobacco did not influence the incidence of arteriosclerosis in the series studied.

There was a definite relation in both sexes between the incidence of hypertension and of arteriosclerosis of the lower extremities.

Women showed a much higher incidence of varicose veins than did men employed in the same occupations. This difference held true even when the factor of pregnancy was removed from the data. Women who had been pregnant showed a higher incidence of varicose veins than women who had never been pregnant. Varicose veins were extremely common among the working women of this series.

Women who stood or walked showed a much higher incidence of varicose veins than those who sat at their work.

This difference was not found in men.

There was a higher incidence of arteriosclerosis of the leg arteries in men with varicose veins. This difference was not statistically established in women.

AUTHORS.

Hertzman, A. B., and Roth, L. W.: The Vasomotor Components in the Vascular Reactions in the Finger to Cold. Am. J. Physiol. **136:** 669, 1942.

The vascular reactions in the finger to chilling have been examined by means of the photoelectric plethysmograph. Analysis of these reactions was concerned with the role of the vasomotor reflexes.

The initial immediate constriction on application of cold is due to vasoconstrictor reflexes on which is superimposed somewhat later the direct constrictor action of cold. Evidence: Accompanying constriction occurs also in the warm control fingers of the same and opposite hands, but the constriction is usually more intense in the chilled finger.

If a vasoconstrictor reflex is not elicited in the control fingers by an application of moderate cold, the constriction in the chilled finger occurs in a gradual progressive manner, as in the forehead skin, due to the direct constrictor effect of cold on the vessels.

The reactive dilatation, which follows in the chilled finger within three to eight minutes after the application of cold, occurs independently of the vasomotor system. Evidence: The dilatation may be limited to the chilled finger and may occur there when the vasoconstrictor tone is high in the control fingers.

Vasoconstrictor reflexes were elicited in the chilled finger during the reactive dilatation in some experiments, while in other instances definite evidence of vasoconstrictor paralysis in the chilled finger was obtained. AUTHORS.

Hertzman, A. B., and Roth, L. W.: The Reactions of the Digital Artery and Minute Pad Arteries to Local Cold. Am. J. Physiol. **136:** 680, 1942.

The selective effects of local cold on the terminal pad vessels and the digital artery of the chilled finger were demonstrated by means of photoelectric plethysmographs.

The digital artery does not participate in the vasoconstrictor reflexes elicited by the cold. Its later constriction during the continued application of cold appears to be due to the direct effects of the fall in temperature on the artery.

The reactive dilatation which appears during the application of cold is limited to the minute pad vessels and does not involve the digital artery until the resultant rise in finger temperature permits relaxation of this artery.

The effects of these reactions on the propagation of the pulse in the finger's arterial system were studied by recording the pad pulses with high frequency galvanometers.

In the usual experiment, the time relations and form of the pad pulses in the chilled finger were altered only moderately and in the direction which would be predicted from the relative participation of the pad and digital arteries in the reactions to cold.

In a few normal subjects, the reactive dilatation produced a pad pulse similar to that seen in chronic hypertension, thus suggesting that one of the factors responsible for the change in pad pulse form in hypertension may be the shunting of blood through direct arterio-venous communications.

AUTHORS.

Nylin, V. G., and Malmstrom, G.: Further Investigation Concerning the Interpretation of Prolonged Circulation Time in Cardiology. Cardiologia 5: 333, 1941.

Research into the circulation time by means of the decholin method showed that in 48 healthy persons the time until the first taste perception set in varies between 8 and 21 seconds, an average of 12 seconds, showing a standard deviation of 3.6. The period of taste perception varies between 7 and 24 seconds, an average of 12.8 seconds, and showed a standard deviation of 4.0.

Examination of the same healthy persons at the same time demonstrated that the circulation time in a recumbent position, when the rest blood quantity is larger, was longer; in a standing position, when the rest blood quantity is smaller, the circulation time was shorter.

This change in the circulation time by altered body position cannot be due to an increase in the minute volume on the basis of "getting up work." The work test demands relatively very heavy work to produce the same shortening of the circulation time as in getting up. Neither can it be explained either by hydrostatic blood dislocation phenomena or by alteration of the pulse frequence, the pulse and minute volume appearing on such alterations of position. The latter fall entirely out of account or are considerably reduced by a mechanical ligaturing of the thigh before the position change. On the other hand, the circulation time on arising from a recumbent position is also shortened after the thigh has been ligatured. The shortening appears to be quantitatively not smaller.

There appears to be a definite correlation between the circulation time and the size of the heart in compensated cases of cardiovascular disease.

AUTHORS.

Hirsch, V. S.: Concerning the Regulation of Blood Flow in the Coronary Artery System of Man and the Possibility of Its Histologic Proof. Cardiologia 6: 31, 1942.

In the human coronary artery system there are small branches, the walls of which contain layers of so-called epitheloid cells, such as have been variously described in the jugular or cushion arteries of other vessel provinces.

The arteriovenous transverse connections supposed from physiologic and clinical facts and demonstrated 30 years ago were confirmed histologically by the proof of arteriovenous anastomoses.

According to our findings there are peculiar relations of the so-called epitheloid cells to the elastic elements of the vessel wall. The proof of these cells, sometimes in the one, sometimes in the other sector of the vessel wall, sometimes inside, sometimes outside a closed elastica interna, and the fact that the elastica itself resolves into lines and dots point to a strong plasticity not only of the epitheloid cells but also of the elastic elements as well. Furthermore, the near local relation of the regulatory arrangement of the nervous apparatus is remarkable.

Generally speaking, the previous observations of blood circulation regulators in both man and animals ensued more or less accidentally, our experiments, however, gave a definite proof of the conditions of the possibility of their delineation. The evidently very sensitive formations found in the small arteries are only definitely provable histologically when one succeeds in fixing the blood before firm coagulation sets in. The result of our research appears, from a general point of view, of great importance for the critical estimation of the observable normal formation of small vessels in a cadaver and in a greater measure of pathologic changes.

AUTHOR.

Nicholson, J. C.: Cardiac Massage. Brit. M. J. **1:** 385, 1942.

The author emphasizes the extreme urgency of this condition, which may arise in any operation, however trivial. The decision of whether to attempt cardiac massage must be made at once, and one must act with utmost speed. Only if this is done is any good likely to ensue.

MCCULLOCH.

Egan, W. J.: Cardiovascular Disease in Industry. Wisconsin M. J. **41:** 217, 1942.

The writer reports his experiences in the management of the industrial personnel. It is his belief that he has reduced the rate of mortality of the employees. He is known to have definitely reduced absenteeism from illness.

AUTHOR.

Lowry, E. F.: Evaluation of Heart Signs in Navy Recruiting. Mil. Surgeon **90:** 37, 1942.

The author describes briefly the usual signs of borderline cardiac disease and disturbances in the recruits.

MCCULLOCH.

Bramwell, C.: Wartime Problems of a Cardiologist (Finlayson Memorial Lecture). Glasgow M. J. **19:** 1, 1942.

A useful résumé in classical form by a real master of the common problems facing selective service boards and cardiologists in the armed service. The problem of accurate diagnosis and classification is really important to the draftee and the service which the examining physician represents.

MCCULLOCH.

Allen, C. R., Stutzman, J. W., Slocum, H. C., and Orth, O. S.: Protection From Cyclopropane-Epinephrine Tachycardia by Various Drugs. Anesthesiology **2:** 503, 1941.

Procaine, carbon dioxide, quinidine, morphine, ergotamine, F 883 (diethyl-amino-methyl-benzo-dioxane), and yohimbine have been studied for the prevention of cyclopropane-epinephrine tachycardia. These agents are all protective in proper dosages. The effective amounts per kilogram when administered intravenously are: procaine, 16 mg.; quinidine, 15 mg.; ergotamine, $\frac{1}{6}$ mg.; F 883, 2.0 mg.; and yohimbine, 0.2 mg. The morphine dose was 8 mg. per kg. when given subcutaneously. Twenty to 24 per cent carbon dioxide in the anesthetic mixture also gave protection.

It is believed that procaine, carbon dioxide, and quinidine give protection from cyclopropane epinephrine tachycardia because of myocardial depression; F 883 and ergotamine, by their sympathicolytic action; yohimbine, through its adrenolytic action; and morphine, by producing either functional decerebration or myocardial depression.

AUTHORS.

Thienes, C. H., Greeley, P. O., and Guedel, A. E.: Cardiac Arrhythmias Under Cyclopropane Anesthesia. Anesthesiology **2**: 611, 1941.

Cardiac arrhythmias occur in cyclopropane anesthesia. These arrhythmias appear at about the beginning of respiratory failure, and are typically of the nature of ventricular extrasystoles.

High concentrations of cyclopropane (50 to 75 per cent in alveolar air), or larger doses of atropine, abolish or minimize these arrhythmias in a large proportion of subjects.

Cyclopropane does not seem to be toxic to the heart, since extreme concentrations failed to produce changes in cardiac activity which we can interpret as muscle depression, except in the presence of anoxemia (experiments on the dog).

A-V nodal rhythm occurred in a small number of human and dog subjects at 70 per cent cyclopropane. Increasing the concentration to 100 per cent resulted in A-V nodal rhythm in most dogs.

An explanation of the effect of high concentrations of cyclopropane on cardiac arrhythmias is suggested.

AUTHORS.

Kaltreider, N. L., Meneely, G. R., and Allen, J. R.: The Effect of Epinephrine on the Volume of the Blood. J. Clin. Investigation **21**: 339, 1942.

Measurements were made at rest of the volume of the blood and its components, and variations in the volumes were followed after the subcutaneous injection of 1 c.c. of epinephrine (1-1000). Further observations included measurements of the blood hemoglobin and viscosity, serum proteins, venous and arterial pressures, velocity of the blood, and pulse rate. These observations lead to the following conclusions:

1. In normal individuals, following the administration of epinephrine, there is a prompt and definite decrease in the plasma volume, which persists in most cases for at least 45 minutes. In the majority of cases there is a slight increase in the cell volume. These alterations are associated with an increase in blood hemoglobin and viscosity and serum proteins. Following the administration of the drug, the systolic pressure increased while the diastolic pressure fell slightly.
2. In individuals who have polycythemia vera with splenomegaly, epinephrine causes a definite decrease in the plasma volume, a moderate increase in cell volume with little change in the total volume.
3. After the injection of epinephrine into 2 individuals whose spleens had been removed, there was a decrease in both blood and plasma volumes, accompanied by a slight decrease in the cell volume.
4. The effects of severe exercise and of epinephrine on the components of the blood volume are similar.

L. W. ROTH.

Dale, U. D., and Jacques, L. B.: The Prevention of Experimental Thrombosis by Dicoumarin. Canad. M. A. J. **46**: 546, 1942.

Intravenous injection of 3, 3 methylenebis (4-hydroxycoumarin), "dicoumarin," increases the prothrombin time of dogs. The administration of this substance in sufficient amounts prevents the formation of intravascular and extravascular thrombi.

This demonstrates an intimate connection between the clotting mechanism and the formation of thrombi (agglutination of platelets). Further, it provides an experimental basis for the clinical use of the material to prevent thrombosis.

Due to its cheapness, its long action, and the fact that it is active on oral administration, dicoumarin possesses many definite advantages for clinical use in the prevention of thrombosis. The long latent period before its effect is demonstrable and the impossibility of terminating this effect quickly may constitute disadvantages. Before its clinical use can be recommended, further studies regarding its toxicity should be undertaken.

AUTHORS.

Flaxman, N.: Digitalis in Arteriosclerotic (Coronary) Heart Failure With Normal Rhythm. J. A. M. A. **119:** 252, 1942.

The action of digitalis on 51 patients with arteriosclerotic (coronary) heart failure with normal rhythm was studied.

The patients were divided into two groups: those with a normal rate (31 or 61 per cent) and those with sinus tachycardia (20 or 39 per cent).

Digitalis was most effective on those with isolated failure of the left ventricle and a normal rate, and least effective on those with combined ventricular failure and sinus tachycardia.

The action of digitalis is primarily on the myocardium and not on the cardiac rate, as noted by the mortality of 6.4 per cent in those with a normal rate and 60.0 per cent in those with sinus tachycardia.

The use of increased amounts of the newer digitalis, U. S. P. XI, only brought on early toxic reactions and had no effect on the mortality.

AUTHOR.

DeGraff, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics. J. A. M. A. **119:** 998, 1942.

The lethal doses for six mercurial diuretics when injected intravenously in the cat so as to kill within twenty to thirty minutes are salyrgan-theophylline 1.11, mercupurin 0.83, mercurin 0.70, salyrgan 0.41, esidrone 0.24, and esidrone without theophylline 0.27. These values are in cubic centimeters per kilogram and have been adjusted to a mercury content of 40 mg. per c.c.

Previous treatment with oral ammonium chloride, oral phenobarbital, intravenous aminophylline, and intravenous digitaline Nativelle had no effect on the lethal dose of mercupurin.

At least in the case of mercupurin, the lethal dose is smaller the slower the rate of injection (or the greater the interval between injections). This suggests (a) that the sudden death following these drugs cannot be avoided by slow injection and (b) that lethal doses of the various drugs should be compared only when the animals die within the average time of interval.

Dilution of the drug is of little value in preventing death from the intravenous injection of mercupurin.

Death is caused by action of these drugs on the heart. An early manifestation is a change in intraventricular conduction while the terminal effect is either ventricular fibrillation or respiratory failure secondary to the cardiac action.

AUTHORS.

Barker, M. H., Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics. J. A. M. A. **119:** 1001, 1942.

In a search for common factors and pertinent points in four deaths following mercurial diuretics the authors note that all four patients had suffered from some

chronic wasting disease. Edema had been present in variable amounts over many months. Each patient had received diuretic salts, chiefly ammonium nitrate and potassium chloride, in variable amounts as a salt substitute. The sequence of events leading to death were similar. Three patients who had had definite cardiac damage received digitalis occasionally, but none were taking it at the time of death. One patient, however, was taking urginin. Two patients had advanced renal disease and a third had moderate cirrhosis of the liver. Three of the patients had received numerous injections of different mercurial diuretics (ranging from fifteen to two hundred) while the nephrotic patient died following the initial dose. To date the authors are unable to correlate the method of administration of the drugs, adjunct mineral diuretic salts or changes in the body chemistry with these fatalities. Because of the wasting of the body tissue, which is striking in the edematous patient, they were unable to exclude a toxic effect of a relative overdose of mercury. Whether in patients or in dogs, death by cardiac arrest is similar, regardless of the type of mercurial compound employed.

AUTHORS.

Brown, G., Friedfeld, L., Kissin, M., Modell, W., and Sussman, R. M.: Deaths Immediately Following Intravenous Administration of Mercupurin. J. A. M. A. **119**: 1004, 1942.

In the cases of congestive heart failure the intravenous injection of 2 c.c. of mercupurin was followed by immediate death.

In 3 of the 4 cases immediate reactions were noted after intravenous injections prior to the final one. These included dyspnea, orthopnea, sweating, pallor, bradycardia, and syncope. In no case was there a delayed reaction such as might be due to massive diuresis, loss of chloride or disturbance of the electrolyte balance. In all the patients a satisfactory but not massive diuresis followed previous injections of mercupurin.

Two of the 4 patients had received intramuscular injections with adequate effect and without toxic reactions on previous occasions.

AUTHORS.

DeGraff, A. C., and Nadler, J. E.: A Review of the Toxic Manifestations of Mercurial Diuretics in Man. J. A. M. A. **119**: 1006, 1942.

Mercurial diuretics are useful drugs, frequently indispensable, and it would be unwise to restrict their clinical application on account of an occasional untoward reaction. It should be borne in mind, however, that these drugs are very potent and they must be used with due consideration to contraindications, associated medication such as digitalis, state of salt and water balance, and previous reactions shown by the patient.

AUTHORS.

Corrigendum

In the November, 1942, issue of the JOURNAL, Vol. 24, p. 629, the article by L. N. Katz et al., in the thirteenth line, should read: . . . when QRS in lead CF_2 had only two phases of the $|\diagdown|$ type which were not less than 3 and 5 mm., respectively, in size; when QRS in lead CF_4 had only two phases of the $|\diagdown|$ type and the upright phase was not less than 3 mm., or when it had only one phase of the $\wedge$ type, or when it had two phases of the $|\diagup|$† type or . . .

†Inverted N.

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A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

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